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HUMAN PHYSIOLOGY

REVISED EDITION

by W. B. Youmans

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UNIVERSITY OF WISCONSIN

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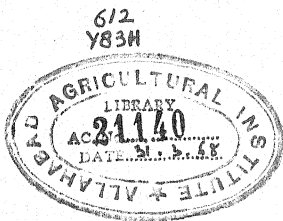
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And therefore we assert that such a course of physiology as is needful for the comprehension of its general truths, and their bearings on daily conduct, is an all essential part of a rational education.

—From *Education*, by HERBERT SPENCER

DEDICATED TO
CYNTHIA, CAROL,
AND GILBERT

Preface

The purpose of this book, like that of the first edition, is to present a standard body of factual information and to help the student achieve an understanding of these facts. The roles of the specific body-maintenance mechanisms that enable it to cope successfully with its environment are explained. Since this approach is used, emphasis is placed on devices for regulation of body processes as well as on the processes themselves. In some instances specific experiments are described so that the student can gain insight into the scientific method as it is used in physiological research.

This edition is somewhat more elementary than the first edition. This has been achieved by eliminating some of the advanced subjects, by rewriting some of the difficult portions, and by adding background information concerning human anatomy. Another change in the book is the expansion of the glossary to make it quite comprehensive. In some instances the glossary contains additional information beyond that presented in the text, and I recommend that the student form the habit of regularly using the glossary when he studies the text.

Three new chapters have been added (Chapters 39, 40, and 41). The mechanisms of inheritance sometimes are covered in courses in physiology, hence it is desirable to have a chapter on this subject in the book. The question of what physiological problems will be encountered in space travel is an interesting and timely subject. It also serves to illustrate how the basic physiologic processes, already described in previous portions of the book, operate under the unusual conditions which will be encountered in a satellite or in a space ship. Chapter 41 also is concerned largely with application of facts already presented.

In the use of this book, the amount of time spent on Chapters 1-6 should be determined largely on the basis of whether the students have had courses in chemistry and biology or zoology. If they have had both, this part may be covered quite rapidly. In any case, this part provides for an equalization of the backgrounds of the students if some have

studied one or the other of these courses while others have not. After study of the first six chapters as needed, Chapters 7-10 should be studied next, since an understanding of the peripheral part of the nervous system, the characteristics of reflex action, and the responses of effectors is necessary in order to comprehend the neural control of the functions of each of the organs of the body. Once Chapters 1-10 inclusive have been studied, considerable variation in the order of coverage of the other chapters is possible. For example, the study of Chapters 11-16 could be deferred. I prefer to take up circulation and respiration (Chapters 17-26) next after Chapter 10 and consider the central nervous system and senses during the last third of the course. One reason for this is that the central nervous system inherently is more difficult to study, and the student is better prepared to cope with it during the latter part of the course. If Chapters 11-16 are deferred they must be studied at least before Chapter 38.

The first edition of this book has been referred to as being "tightly written." To a lesser degree this is true also of the present edition. This statement is related mainly to the fact that the book contains relatively few filler sentences; hence the amount of information presented is greater than is found in most textbooks of this size. The student may find the first reading of most parts of the book to be a little more difficult than most texts, but on the second reading or review he will be spared the necessity of sorting out the informative sentences from filler sentences. I have adhered to this approach because I believe that the modern college student prefers to have his time conserved.

Acknowledgments. I wish to express my appreciation to my wife, Cynthia, my daughter, Carol, and the secretary of the Department of Physiology, Mary Hood, for secretarial assistance. Yearbook Publishers have kindly granted me permission to use some illustrations from my book, *Basic Medical Physiology*, copyright 1952. I am indebted to a number of other publishers for permission to reprint figures, and the acknowledgments of the sources of these figures are included in the legends. Again, I wish to acknowledge my indebtedness to my major professor, Walter J. Meek, Emeritus Professor, at the University of Wisconsin, whose example of effective and inspiring teaching of physiology at both the undergraduate and graduate levels has stimulated my interest in attempting to organize physiologic information for presentation to students.

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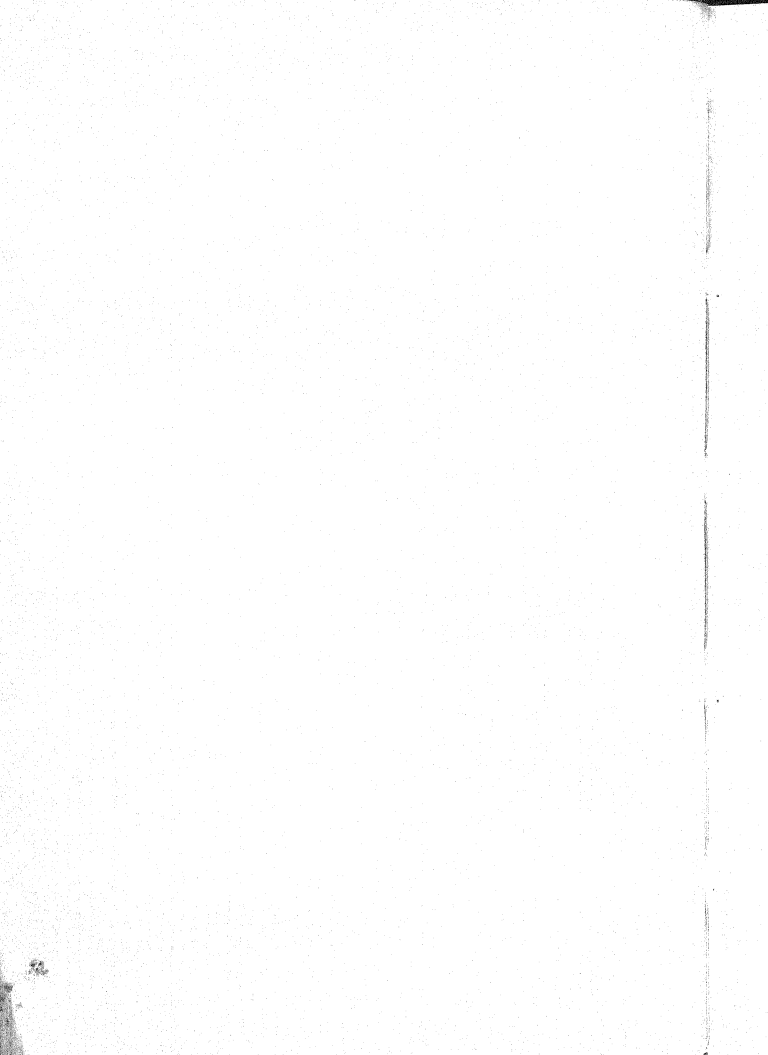
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Chapter 1

LIFE PROCESSES AND THE CELL

Physiology: The Study of Life Processes

Physiology is the science which deals with the functioning of living organisms. Although in this book we are concerned specifically with the functioning of the human body, or Human Physiology, there are few processes occurring in man which do not have a counterpart in other species. Furthermore, some processes are common to virtually every living cell, whether the cell constitutes the entire organism or whether it is one of the cells of a multicellular organism. Therefore, the student of human physiology must become familiar with certain aspects of cellular or general physiology, and he is interested also in vertebrate physiology, especially mammalian, because of the structural and functional similarities between man and the higher animals.

Biology is the science which deals with life in all of its manifestations, hence physiology is one of the biological sciences. One who studies living organisms may be interested in classification (taxonomy), structure (morphology, anatomy), or function (physiology). The important background sciences for the study of human physiology are anatomy, physics, and chemistry. Physiologic processes occur in specific structures; therefore, any course in physiology either must follow a course in anatomy or must include some instruction in anatomy. However, a great amount of detailed knowledge of anatomy is not necessary for an understanding of the major physiological principles. You can acquire the essential anatomical information as you proceed with the study of physiology.

The processes with which physiology deals may be explained most readily in the language of chemistry and physics. Physics deals with transformation of energy, and chemistry deals with transformation of matter; however, the two sciences actually are inseparable since transformation of matter is accompanied by energy changes in the form of

heat, light, etc. It is quite desirable that a student beginning the study of physiology have a background in biology and chemistry. If not, it will be essential for him to preface his study of physiology with a study of some elementary chemical and biological principles such as are covered in Chapters 1 and 2 of this book.

Characteristics of Living Matter

Living matter exhibits a great variety of processes and activities. The living organism is capable of maintaining itself as a unit, of reproducing itself, of growing and developing, and of adapting itself to its environment. On the anatomical side, it has a characteristic organization. If a mammal, for example, it is bilaterally symmetrical, has four appendages, a diaphragm, and four-chambered heart; if it is an organism consisting of a single cell, it has characteristic organelles.

The principal properties that generally are listed as being characteristic of living matter are (1) *metabolism*, (2) *growth*, (3) *reproduction*, (4) *adaptability*, and (5) *characteristic organization*.

The term *metabolism* literally means to "change over." It refers to all of the numerous chemical reactions which occur within the organism. Living organisms take up substances from the environment, convert some of these into compounds essential for structure or function, and excrete substances which are not needed.

The striking feature in growth of the living organism is that it produces more of itself. Reproduction, the production of a new organism, may be considered to be a specialized phase of growth.

Adaptability refers to the ability of the organism to undergo alterations which make it better adjusted to its environment. As the environment is altered the organism shows changes, either immediately or after some delay, and these changes are such as to improve its chances of survival.

Although it is easy to distinguish between the living and the non-living in most instances, it is difficult to draw a precise boundary line between the simplest living organisms and the non-living. For example, whether *filterable viruses* should be considered as living or non-living has been disputed for a long time. Viruses are so small that they will pass through a porcelain filter. Their structure is very simple, as shown in Figure 1-1, but they are capable of growth providing they are associated with the more complex living organisms. It is noteworthy also that no sharp divid-

ing line can be drawn between the simplest plants and animals. A single-celled organism, *Euglena*, is described in both zoology (animal biology) and botany (plant biology) textbooks. Movement is one of the distinguishing features of animals, and ability to carry on photosynthesis

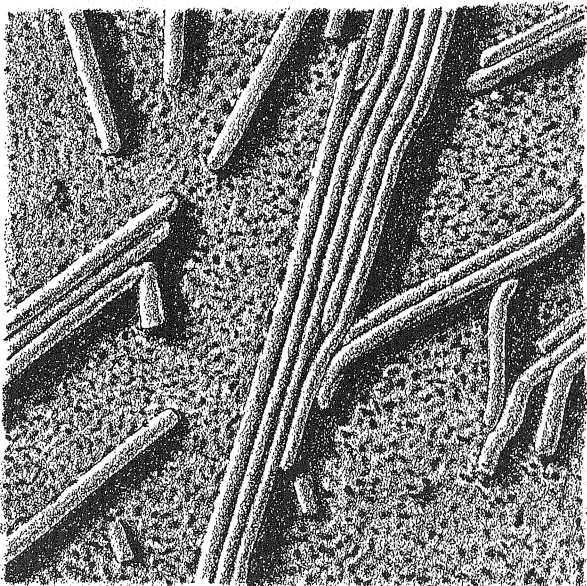


Figure 1. Tobacco mosaic virus.

Magnified 100,000 times by the electron microscope.

through the action of chlorophyll is characteristic of plants; but *Euglena* possesses both of these attributes.

A characteristic feature of the living organism is that it is composed of one or more *cells*. Again this is true except for the border-line cases. The characteristics of cells are described below. Some organisms consist of a single cell; however even when the organism, like man, is large and

multicellular, all characteristic life processes occur within cells. In other words, everything from the simplest to the most complex reaction within the body, whether it be the beat of the heart or the remembering of an incident that happened many years ago, occurs in or as a result of the activity of cells. This means that if we fully understood life processes we could explain them in terms of cellular functions.

Included in characteristic organization also is the fact that certain types of compounds typically are found in living matter. Some of these substances are inorganic; others are carbon-containing compounds produced by the organism and are known as organic compounds.

A striking characteristic of the living organism is that it acts upon its environment and in turn it reacts to the surroundings in such a way as to make it better able to survive. Some of the reactions of organisms to the environment are instantaneous and evanescent, while others are quite gradual and persist for a long time. The immediate reactions are exemplified by reflexes which are important in the control of all body processes. An example of a reflex is the involuntary withdrawal of the hand when it comes in contact with a hot object. Slower adaptations or adjustments commonly are referred to as acclimation. A well-known example of this is the increased ability to withstand the rarefied air at high altitude which results when the individual remains there for a few weeks.

Finally a characteristic of life which is expressed over long periods of time is its ability to evolve—to give rise to new forms which are better adapted for survival; hence the living organisms now in existence exhibit remarkable adaptation to the conditions which they must encounter. In the process of long-term adaptation those mechanisms which are of use to the organism (that is, have survival value) have been retained and, for the most part, mechanisms as well as structures which are of no use have become vestigial or lost.

Characteristics of Cells

The cell theory. In 1665 Robert Hooke presented before the Royal Society of London his classic paper on *The Texture of Cork by Means of Magnifying Lens* in which he referred to the individual units of cork as *cells*. He was observing only the "skeletons" of cells, but it is now well known that living organisms consist of one or more units or cells and of varying amounts of intercellular material laid down by them. The rela-

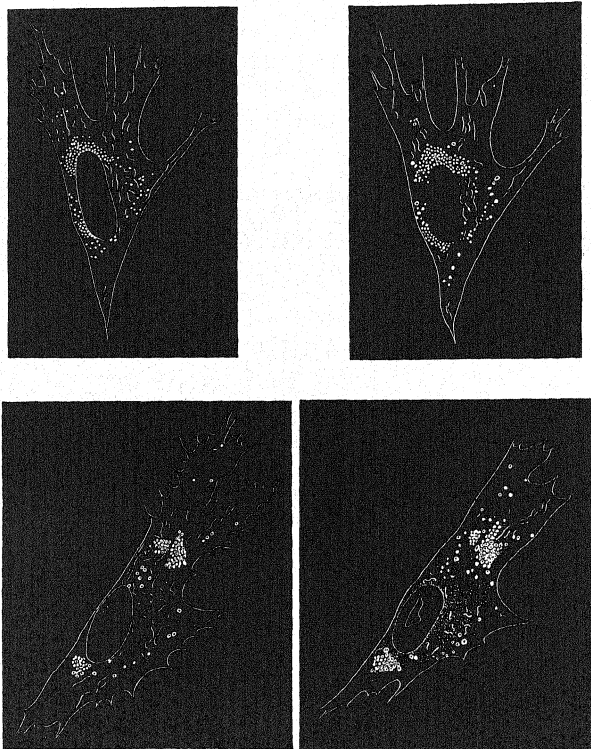


Figure 1-2. Cells before and after fixation.

Above, left—Normal living cell. *Above, right*—Slight changes produced by fixation with 2% osmic acid. *Below, left*—Normal living cell. *Below, right*—Changes produced after fixation with Flemming and acetic acid. (Reproduced by permission from Gray, *Textbook of Experimental Cytology*. Copyright, 1931, by Cambridge University Press.)

tively complex living material which is contained within the cell is known as *protoplasm* (Gr. *protos*, first, and *plasma*, formation). The complex multicellular organism, which is composed of many types of cells, develops from a single cell by repeated division, growth, and differentiation. Groups of more or less similar cells, along with intercellular substance laid down by them, form *tissues*. The tissues are combined in characteristic patterns to produce *organs* such as the heart, lungs, and liver. The science which deals with the structure and functions of cells is known as *cytology* and the study of the structure of tissues is *histology*, while *microscopic anatomy* deals with the minute structure of the organs.

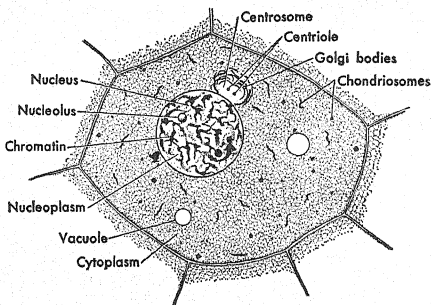


Figure 1-3. Diagram of the parts of a generalized tissue cell.

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Methods of studying cells. Unicellular organisms may be observed in their natural environment, and living cells which have been removed from multicellular animals may be kept alive for a prolonged period and may grow if they are placed in appropriate solutions; hence they also may be studied under the microscope. Despite the complexity of cells the composition of some of the nutrient solutions used for the culture of them is comparatively simple.

Animal cells, typically, are composed of a cell body, or *cytoplasm*, and a *nucleus*. The boundary of the cytoplasm is called the cell wall. Cells show a wide degree of variation in size and shape of the nucleus and cytoplasm, and some cells lay down large quantities of material outside

the cell wall while others produce no intercellular material. Observations of the nucleus and cytoplasm usually may be made in a living cell that has received no special treatment. Inclusions in the nucleus or cytoplasm may be accentuated or made visible by staining. Some stains can be

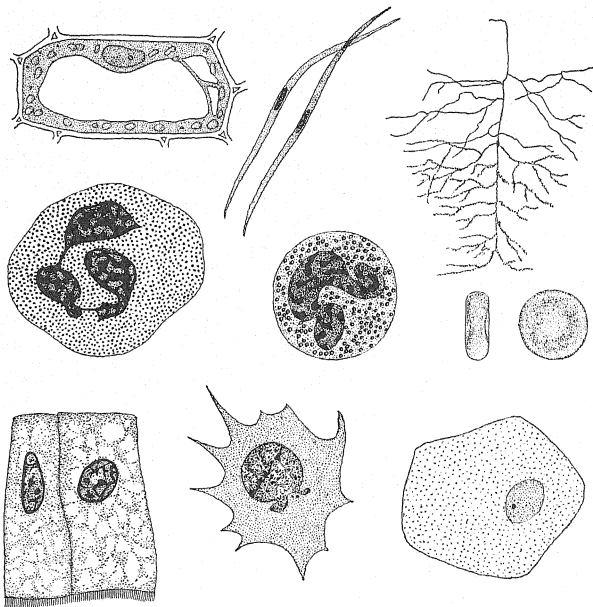


Figure 4. Drawings of different types of cells as they appear under the microscope.

The cells are not drawn to the same scale.

introduced into the living organism and, depending upon their composition, become concentrated in certain structures. On the other hand, dyes may be applied directly to isolated surviving cells or tissues.

In histological studies usually, the tissues are killed, or "fixed," by

appropriate solutions and subsequently are treated with stains. Most of the fixatives which are made use of precipitate the protein of the cell; then the tissue either is frozen or it is infiltrated with gelatin, paraffin, or celloidin which later solidifies so that the matrix and embedded tissue may be sliced into very thin sections. Finally, the thin slices are placed on a glass slide and treated with one or more stains.

Parts of the cell. The typical cell consists of cell wall, cytoplasm, and nucleus. *Protoplasm* includes all of the living material within the cell. The microscopic appearance of the protoplasm varies with the treatment it receives prior to examination; it may appear as a reticulum (network) or as fibrils (fine threads) or it may be granular or alveolar (foamy) in appearance. The nucleus frequently contains a round, distinct body, the *nucleolus*, and there are smaller irregular masses called *chromatin granules* which seem to be suspended on a fine reticulum, the *linin network*. Cytoplasm contains various formed constituents depending on the type of cell. Some of these grow and divide prior to division of the cell. They include the *mitochondria*, the *Golgi apparatus*, the *centrioles*, and *fibrils*. In addition to the *organoids* just listed, various lifeless *inclusions*, which are accumulations of organic compounds, crystals, secretion granules, etc., may be seen in some cells.

Cell Division

When a cell divides the chromatin in the nucleus becomes equally distributed between the two daughter cells. This is accomplished according to a definite series of changes illustrated in Figure 1-5. The entire process is known as *mitosis*. In the resting cell the chromatin material appears as granules arranged in a network. As the cell begins the process of division it is noted that a small body on the outside of the nucleus, known as a centriole, divides first, and the two centrioles move away from each other. At the same time the chromatin granules begin to be arranged in definite threads. The threads of chromatin are the chromosomes which are found in a characteristic number for each species. The chromatin particles making up the chromosomes represent groups of *genes* which are arranged in a specific linear order in each chromosome. The gene is considered to be the physical unit by which transmission of traits from parent cell to daughter cells is accomplished; it is the physical basis for inheritance. It is necessary, therefore, in the process of mitosis that each

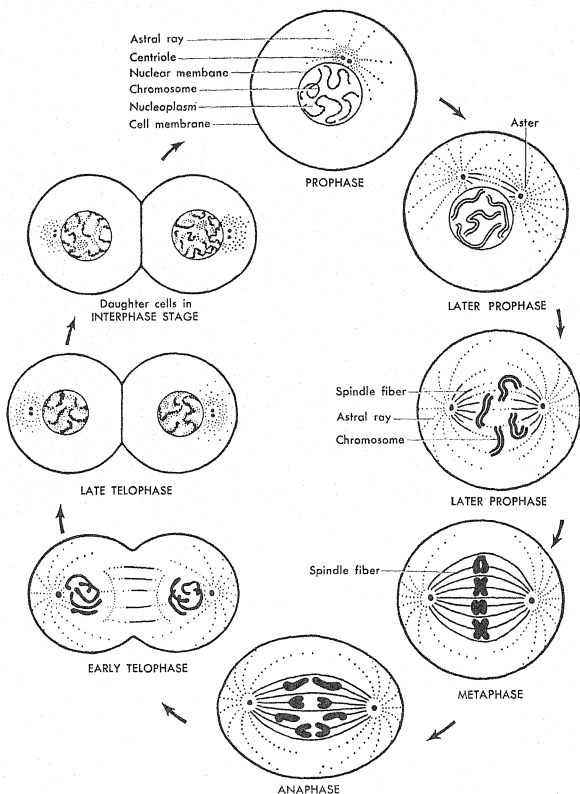


Figure 1-5. Stages in cell division.

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gene divide into two daughter genes and that one of these appears in each of the daughter cells.

Shortly after the chromosomes become visible as slender threads they begin to shorten and thicken, then they appear to split longitudinally. At this stage it is believed that the individual gene grows and splits into two replicas of the original. By the time that the splitting of the chromosomes is evident, the centrioles have reached opposite poles of the cell, the nuclear membrane has disappeared, and rays can be seen extending between the centrioles to form a spindle-like figure. Next the chromosomes become aligned across what would be the equator of the cell (when the centrioles represent the poles). This is called the equatorial plate stage. Then the daughter chromosomes pull away from each other and one moves toward each centriole. When a set of daughter chromosomes has become accumulated at each pole of the cell the cytoplasm becomes constricted so that a separate mass surrounds each group of chromosomes, and at the same time a nuclear membrane forms to enclose the chromosomes in each of the new cells. Finally, the chromatin material becomes dispersed as in the resting cell and the cycle is complete.

Although cell division is a continuous process, frequently it is subdivided for descriptive purposes into four stages (Figure 1-5). The *prophase* is the initial part of the process, the equatorial plate stage is the *metaphase*, the *anaphase* includes the movement of the chromosomes to opposite poles, and the *telophase* includes the remainder of the process by which the two complete daughter cells are formed.

Chapter 2

INTRODUCTORY PRINCIPLES

General Chemical Principles

Particulate nature of matter. *Atom*, meaning indivisible, refers to the smallest unit of matter which can enter into chemical combination to form compounds. Certain substances found in nature are called *elements*. The smallest units of such substances are the atoms. Chemical combinations result when atoms of opposite electrical charge are brought together. In such combinations a fixed amount of any one element combines with a fixed amount of one or more other elements, and the substance produced is known as a *compound*.

Each element is designated by a symbol which usually is a letter or two of its name. In some cases the symbol is derived from the Latin name of the element (e.g., Fe for iron and Na for sodium). The *atomic weight* is the relative weight of an atom of a substance when compared with some element as a standard. In the table of atomic weights, hydrogen, which is the lightest atom, is listed as 1.008 and the weights of the other atoms are given on the same scale. For example, weight of oxygen is 16, meaning that an atom of this substance is about 16 times as heavy as hydrogen.

The atoms which are found in the human body, together with their symbols and atomic weights, are listed below.

ELEMENT	SYMBOL	ATOMIC WT.
Calcium	Ca	40.07
Carbon	C	12.00
Chlorine	Cl	35.46
Cobalt	Co	58.94
Copper	Cu	63.57
Fluorine	F	19.00
Hydrogen	H	1.008

ELEMENT	SYMBOL	ATOMIC WT.
Iodine	I	126.93
Iron (Ferrum)	Fe	55.84
Magnesium	Mg	24.32
Manganese	Mn	54.93
Nitrogen	N	14.008
Oxygen	O	16.000
Phosphorus	P	31.03
Potassium	K	39.10
Sodium (Natrium)	Na	23.00
Sulfur	S	32.06
Zinc	Zn	65.38

Although 18 elements are listed, 99 per cent of the total weight is due to 6 of them as follows: oxygen, 65 per cent; carbon, 18 per cent; hydrogen, 10 per cent; nitrogen, 3 per cent; calcium, 2 per cent; and phosphorus, 1 per cent. Potassium, sulfur, sodium, and magnesium together account for about 0.8 per cent of the body weight. The remaining substances constitute only about 0.2 per cent of the total body weight.

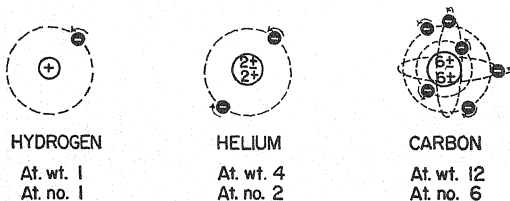


Figure 2-1. Diagrammatic representation of the structure of the hydrogen, helium, and carbon atoms.

The hydrogen atom is the simplest of all atoms; its nucleus contains one proton, indicated by +, and one electron, indicated by -, moves in an orbit around the nucleus. The carbon atom is shown as having six protons and six neutrons (\pm) in the nucleus with six electrons moving in orbits around the nucleus. Atoms of higher atomic weight (At. wt.) and atomic number (At. no.) are correspondingly more complex in structure.

Atoms are composed of several types of particles. Among these are negatively charged particles called *electrons*, positively charged particles called *protons*, and *neutrons*, which have no charge. As shown in Figure 2-1, the atom contains an equal number of protons and electrons. Protons and neutrons are found in the nucleus of the atom, while the electrons are found in shells surrounding the nucleus.

Most matter is in the form of compounds which are produced by the

union of two or more elements in characteristic proportions. Water, for example, is a compound, each molecule of which contains two hydrogen atoms and one oxygen atom; hence the water molecule is designated by the symbol H_2O . A *molecule* is the smallest unit of a compound.

Each element has a characteristic number of bonds or valences. Valence is expressed as the number of hydrogen atoms replaceable by a given atom. Thus hydrogen itself has a valence of one. Oxygen has a valence of two, and the formula for H_2O also can be written $\text{H}-\text{O}-\text{H}$ to designate the bonds.

Solutions. When compounds go into solution in water either the individual molecules become dispersed throughout the solution, as for example, sugar; or the molecules break up into positively and negatively charged particles called *ions*, as for example sodium chloride (Na^+, Cl^-). The dissociation of a compound into ions is called *ionization*. The positively charged ions are called *cations* and negatively charged ions are called *anions*.

When a solid is dissolved in a liquid, the latter is called the *solvent*, and the dissolved substance is called the *solute*. If particles in solution are of a comparatively large size, namely, from one 39 billionth to one 7800 billionth of an inch, the mixture is called a *colloidal solution*. If the particles are larger than this, the mixture is called a *suspension*.

When two liquids, for example alcohol and water, are mixed together they may become molecularly interspersed. Such liquids are said to be *miscible*. A clear solution is formed and a sample may be removed to determine the proportion. When immiscible liquids are mixed, an *emulsion* is formed, one of the liquids being suspended as droplets in the other. The former liquid in this case constitutes the *discontinuous* phase and the latter, the *continuous* phase. Under certain conditions the phases may become reversed, the continuous phase becoming the discontinuous phase, and this change may be associated with a decrease in fluidity. The colloid in the more fluid state is called a *sol* and in the less fluid, or congealed state, a *gel*. Protoplasm is a very complex substance both physically and chemically. It is a colloidal solution with smaller particles dissolved in it and larger particles suspended in it.

Composition of Protoplasm

Organic compounds are the more complex carbon-containing substances. All other substances are classified as *inorganic*. Hydrogen,

oxygen, and nitrogen are the chief elements which, in addition to carbon, are found in the organic compounds, and sulfur, phosphorus, and iron sometimes are present.

Water (H_2O) makes up about two-thirds of the body weight. In some lower forms of life an even higher fraction of the body is water. It is the medium in which the ions and molecules move and the numerous metabolic reactions occur. Also, many of the chemical reactions of the body involve either the uptake or liberation of water molecules.

A number of kinds of cations and anions are present within the cells and in the fluid between cells and in the blood plasma. These include sodium (Na^+), potassium (K^+), calcium (Ca^{++}), magnesium (Mg^{++}), chlorides (Cl^-), sulfates (SO_4^{--}), phosphates (PO_4^{---}), and carbonates (CO_3^{--}).

Principal organic constituents. Three classes of organic compounds regularly are found in protoplasm in relatively large amounts: *carbohydrate*, *protein*, and *fat*. These are also the major foodstuffs which are required by the human body. Their principal distinguishing characteristics will be described here, while further consideration of utilization of these compounds will be deferred until the study of digestion and metabolism.

Carbohydrates. Carbohydrates are composed of carbon, hydrogen, and oxygen. As in water, hydrogen and oxygen atoms are present, generally, in the ratio of 2 to 1. Carbohydrates are subdivided into three main groups, *monosaccharides*, *disaccharides*, and *polysaccharides*.

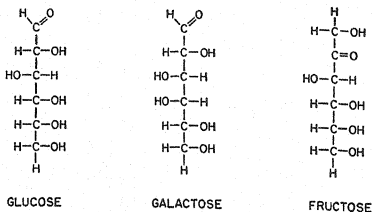
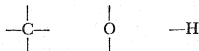


Figure 2-2. Structural formulas of three hexoses.

The monosaccharides include the simple sugars containing two to six carbon atoms and a corresponding number of H_2O 's. They are named dioses, trioses, tetroses, pentoses, and hexoses, respectively. The most

important, physiologically, are *hexoses* (*hexa*-six) having the formula $C_6H_{12}O_6$ (glucose, fructose, galactose). In the above formulas it may be noted that the carbon atoms always have 4 bonds, oxygen 2, and hydrogen 1.



No digestion of the six-carbon sugars is necessary prior to their absorption from the small intestine. After ingestion they dissolve and pass, as such, into the intestinal epithelium. The sugar in the blood is glucose.

A disaccharide is a compound which is formed by the union of two hexose molecules. A molecule of water is liberated in the process. This type of chemical reaction, known as *dehydration synthesis*, is illustrated below.



The general formula for disaccharides is $C_{12}H_{22}O_{11}$ ($2 \times C_6H_{12}O_6$ minus H_2O). Many of the sugars ingested are of this type (sucrose or cane sugar, maltose or malt sugar, and lactose or milk sugar). The di-

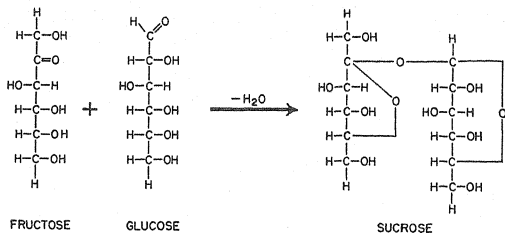
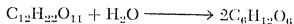


Figure 2-3. Reaction between a molecule of fructose and a molecule of glucose to produce a molecule of sucrose.

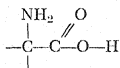
A molecule of water is split out in the process, hence this is a dehydration synthesis.

saccharides are split into simple sugars by digestive processes prior to absorption. This type of reaction, in which a molecule of water is used, is an example of a *hydrolytic reaction*.



Large carbohydrate molecules are built up in plants and animals through combination of many hexose units by dehydration synthesis. These substances are known as *polysaccharides*. They are represented in animals by glycogen and in plants by dextrins, starch, and cellulose. Glycogen is found in largest amounts in liver, muscle, and brain. Cellulose is not digestible; the other three substances can be broken down to glucose in the gastrointestinal tract by the action of digestive enzymes.

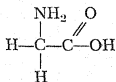
Proteins. The essential structure of the soft parts of the body consists largely of protein. Protein contains carbon, hydrogen, oxygen, nitrogen, sulfur, and sometimes phosphorus. Proteins are built up from amino acids. There are twenty-odd different amino acids most of which contain only carbon, hydrogen, oxygen, and nitrogen. The group or radical common to all amino acids is as follows:



The characteristic feature is an NH_2 group on the carbon atom adjacent to the *carboxyl* (COOH) group.

The NH_2 group is the *amino* group; and the $-\text{COOH}$ group identifies the compound as an organic acid, since ionization occurs yielding a positively charged hydrogen ion. The simplest organic acid HCOOH ionizes

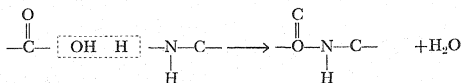
into H^+ and $\text{C}=\text{O}-\text{OH}^-$. Glycine is the simplest possible amino acid since it includes the carboxyl group and, on an adjacent carbon atom, an amino group with the other two bonds of the carbon atom being occupied by hydrogen.



Most protein molecules are large, since they are made up of a considerable number of amino acid molecules. The amino acids are combined in different numbers and proportions to produce protein molecules; therefore there are many kinds of natural proteins. Variation occurs within the individual and from one individual to another and between species. There is evidence that every species has some protein peculiar to itself.

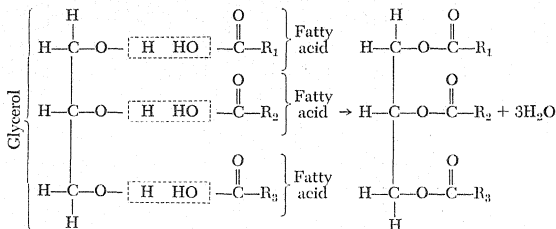
Proteins are built up in the plant and animal by the joining of amino acids through what is called the *peptide linkage*. The OH , or hydroxyl

group, of the carboxyl group of one amino acid molecule combines with a hydrogen atom of the amino group of another amino acid molecule. A molecule of H_2O is split off and the amino acid molecules are linked as shown below.



When protein is ingested by man the peptide linkage is broken by digestive enzymes. The reverse of the above reaction occurs, and the amino acids are absorbed from the digestive tract to be rearranged into the proteins characteristic of the tissues of the human body.

Fats. Fats are composed of carbon, hydrogen, and oxygen, the oxygen being present in smaller amount, relative to carbon and hydrogen, than in carbohydrates. Each molecule of fat is composed of one molecule of glycerol and three molecules of fatty acid. The reaction is as follows, where R is a carbon chain as found in the fatty acids. The R's may all be alike or each may be different.



This is a dehydration synthesis in which one molecule of glycerol and three molecules of fatty acid are used and three molecules of water are split off for each molecule of fat produced. Since there are 18 or more fatty acids, many kinds of fats may be synthesized.

Generally, in protoplasm a molecule of fat is combined with one or more molecules of another compound to form a more complex substance. *Lipid* is the term used to include fats in both the simple and combined form. Carbohydrates and proteins likewise are found combined with other substances.

Organic compounds present in small amounts. It is necessary to distinguish the cell constituents which are present in relatively large amounts, and which make up the structure of the body or are used as the fuel supply of the cell, from other substances essential to the normal functioning of the cell, but present in small quantity. In the latter category are included vitamins, hormones, and enzymes. These three classes of substances include a large group of chemicals, and the nature and actions of many of these substances will be considered later in appropriate sections. Only their principal distinguishing features are presented here.

Vitamins are organic compounds which are required by the body to carry on its normal functions, but which are not produced by the body. If any one of the vitamins is not included in the diet in adequate amounts, the deficiency becomes manifest by the appearance of characteristic signs and symptoms. A vitamin is further characterized by the fact that it is not used as a building material for body tissue or as a source of energy.

Hormones are more or less complex organic substances synthesized by the endocrine, or ductless, glands and liberated into the blood stream to be carried to the sites of action. Hormones are essential for the normal functioning of cells. Deficiency or excess of any of the hormones becomes manifest by the development of characteristic signs and symptoms.

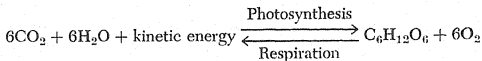
Enzymes are substances concerned with promoting or influencing the speed of chemical reactions. They are complex substances, either protein in nature or intimately associated with protein, which are produced by the cells. The general characteristics and properties of enzymes are discussed in the next chapter.

Many other substances, some of which will be considered later, are present in tissues in small quantities. A number of these are waste products; others are produced at intermediate stages in metabolic processes. Some of these substances may accumulate in considerable amounts if, by the use of suitable enzyme poisons, a metabolic process is stopped at an intermediate stage.

Sources of Energy for Cellular Processes

Living cells take up oxygen from the environment and obtain energy through the action of oxygen upon organic compounds in the cell. Organic compounds are potential sources of energy, and the oxidation of carbon compounds typically results in the liberation of energy; *potential* energy

is converted into *kinetic* energy. Such a reaction is *exothermic* and the reverse type of reaction is *endothermic*. Photosynthesis, which occurs in green plants, is an example of an energy-storing reaction in which light is the source of energy.

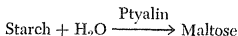


The glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) which is produced possesses potential energy. Cellular respiration is depicted by the reverse of this equation. Numerous exothermic and endothermic reactions occur in the animal body continuously, but the exothermic reactions predominate; therefore, the overall result is *catabolism*, or the breakdown of complex organic substances into simpler substances with the liberation of kinetic energy. In green plants *anabolism* is predominant; simple compounds are converted into more complex substances which are rich in potential energy.

Enzymes and Enzymatic Action

A *catalyst* is defined as a substance which alters the rate of a chemical reaction and which can be recovered when the reaction is completed. *Enzymes* are catalysts produced by living cells. Many of the chemical reactions which occur within cells are brought about through the action of enzymes. In fact, for life to exist a number of enzymes must be present to bring about energy-yielding reactions and to catalyze reactions concerned with the transfer and use of the energy. It has been estimated that protoplasm contains a hundred or more enzymes. Some two dozen which have been isolated in crystalline form have been shown to be protein, and it is possible that all enzymes are protein. In fact, a considerable part of the soluble protein contained in cells consists of enzymes.

Properties of enzymes. Each enzyme has a specific action; like a key opening a lock, it acts upon one substance or upon one particular chemical grouping. The chemical acted upon by the enzyme is known as its *substrate*; and, commonly, the name of the enzyme is written above the arrow in the equation which indicates the reaction. For example, ptyalin, a constituent of saliva, is an enzyme which promotes conversion of starch to maltose.



Enzymes act by combining with their specific substrate to form a complex which is capable of undergoing the particular reaction catalyzed by the enzyme; then, the enzyme is liberated again when the final products are produced. It is estimated that one molecule of an enzyme may cause 300 to 400 molecules of its substrate to react each second at body temperature.

Enzymes catalyze a reaction in either direction; hence they promote the development of an *equilibrium*. For example, if the reaction of A with B is catalyzed to produce C and D, the reaction will go "to the right" when A and B are present in large amounts, and if C and D are present in large amounts they will be acted upon by the enzyme to produce A and B.



As the end products of the reaction accumulate, and hence equilibrium is approached, the rate of the reaction progressively decreases. The above equation also illustrates another characteristic of reactions promoted by

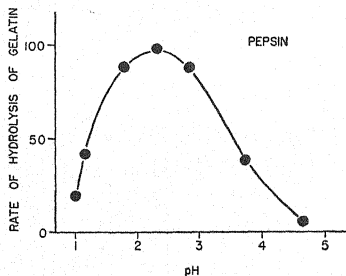


Figure 2-4. The optimum pH for the digestion of gelatin by the enzyme pepsin.

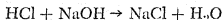
The rate of hydrolysis of gelatin was determined at the seven different pH levels which are graphed while other factors, such as concentration of the gelatin, concentration of pepsin, and temperature were kept constant. The most rapid rate of digestion occurred at a pH of 2.3; this is taken as 100 so that the rates at the other pH's can be read as the per cent of the optimum.

enzymes, namely, that for every molecule of the substrate that disappears one molecule of the specific product appears. This is a higher level of efficiency than is attained in many of the chemical reactions which are not controlled by enzymes.

The activity of an enzyme is studied usually by determining the rate of the reaction which is influenced by it. Thus ptyalin can be added to a given amount of starch and either the rate of decrease in starch concentration or the rate of production of maltose can be determined. By means of such studies it is demonstrated that there are *optimal* conditions for the activity of each enzyme, namely, conditions under which the enzyme converts the most substrate per unit of time. There is an optimal temperature, acidity, concentration of substrate, etc. The influence of pH on the activity of the enzyme pepsin is shown in Figure 2-4. The optimum pH for this enzyme is around 2.3.

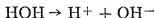
Hydrogen Ion Concentration in Body Fluids

Acids are compounds which dissociate in solution to yield hydrogen ions. For example, when hydrochloric acid (HCl) is put into water it dissociates into H^+ and Cl^- . Bases yield hydroxyl ions when put into solution. Sodium hydroxide (NaOH) yields Na^+ and OH^- . When an acid and a base are mixed they react with each other to produce water and a salt.



If equimolecular portions of HCl and NaOH are mixed, neutralization results and there is no excess of OH^- over H^+ in the solution.

Some of the molecules in pure water dissociate into ions. The equilibrium established is indicated by the equation



The *number* of hydrogen ions equals the number of hydroxyl ions, but the *weight* of the latter is 17 times as great as the former, since the molecular weight of hydrogen is 1.008 and the molecular weight of oxygen is 16. The number of molecules dissociated is such that 1000 gm. (1 liter) of water contains 1/10,000,000 gm. of H^+ ions and 17/10,000,000 gm. of OH^- ions. The value for hydrogen ions is expressed as 10^7 . There is no excess of either H^+ or OH^- , hence water is neutral. The concentration of hydrogen ions in a neutral solution is expressed as cH^7 and hydroxyl ions cOH^7 . The symbol, pH, is the negative logarithm of the hydrogen ion concentration; thus cH^7 becomes pH 7. A table indicating the pH of solutions of various normality is shown below. A normal solution of an

acid contains one gram of replaceable hydrogen per liter, and a normal solution of base contains 17 ($16 + 1$) gm. of replaceable OH^- per liter.

	NORMAL	pH	IF IONIZATION IS ASSUMED TO BE COMPLETE
Acid	1.0	0	
	.1	1	
	.01	2	
	.001	3	
	.0001	4	
Neutral	.00001	5	
	.000001	6	
	.0000001	7	
	.0000001	8	
	.00001	9	
Alkaline	.0001	10	
	.001	11	
	.01	12	
	.1	13	
	1.0	14	

It should be noted that pH 7 indicates that the solution is neutral, and a change of one unit indicates a tenfold change in reaction; for example, a solution of pH 5 is 10 times as acid as a solution of pH 6, and a solution of pH 9 is 10 times as alkaline as a solution of pH 8.

The expression, pH, is for convenience in considering fluids having a reaction near the neutral point, as is the case with biological fluids. The pH of blood is around 7.4 and varies from this by only a few tenths of a pH unit even in diseases which severely affect the reaction of the blood. On the other hand, slight changes in pH are associated with striking changes in body functions. The composition of the blood is such as to buffer changes in pH, and the body has several compensatory mechanisms which serve to counteract changes in pH. A relatively high concentration of hydrogen ions is found in the juice produced by the acid-secreting cells of the gastric glands; the pH of this juice (0.9 – 1.2) is near that of .1 normal hydrochloric acid.

The Gas Laws

According to the kinetic theory molecules of gases, like molecules in solution, are in constant random motion and this is the basis for many of the physical properties of gases. Each gas has its own characteristic molecular weight: oxygen 32, nitrogen 28, carbon dioxide 44, etc. The

gram molecular weight of a substance is the weight in grams which is numerically equal to the molecular weight of the substance. One gram molecular weight of any gas occupies the same volume as one gram molecular weight of any other gas at a given temperature and pressure. Also, the same number of molecules will be contained in this volume.¹ Since a specific quantity of gas will change volume with changes in temperature and pressure, it is necessary to state the volume in terms of standard conditions, namely zero degrees centigrade and a pressure of 760 mm. of

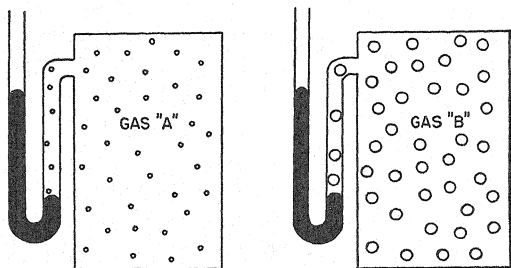


Figure 2-5. Diagram illustrating that equal numbers of molecules of different gases, represented by small circles and large circles, confined in the same space at the same temperature exert the same pressure.

mercury (atmospheric pressure at sea level). The volume of a gas can be measured at any convenient temperature or pressure and corrected by calculations to standard temperature and pressure (STP). At zero degrees centigrade and a pressure of 760 mm. of mercury, one gram molecular weight of a gas occupies 22.4 liters. Conversely, if one gram molecular weight of a gas is confined in a space of 22.4 liters at 0°C. it will exert a pressure of 760 mm. of mercury.

The pressure exerted by a gas is related to the number of molecules occupying a given space regardless of the kind of molecules. Thus, when gases are mixed, each exerts its own pressure independently of the others providing there is no chemical reaction between them (Dalton's or Henry's law). For example, if one-half of a gram molecular weight of oxygen (16 gm.) and one-half of a gram molecular weight of nitrogen

¹ The number of molecules in one gram molecular weight of a gas, known as Avogadro's number, is 6.023×10^{23} .

(14 gm.) are placed in a space of 22.4 liters at $0^{\circ}\text{C}.$, each gas will exert a pressure of 380 mm. of mercury, and the total pressure will be 760 mm. of mercury. In a mixture of gases, such as atmospheric air, the fraction of the total pressure exerted by any one of the gases is called the *partial pressure* or *tension*. Air contains 21 per cent oxygen, and the atmospheric pressure at sea level is 760 mm. of mercury; therefore, the partial pressure of oxygen at sea level, obtained by multiplying 760 by .21, is approximately 160 mm. of mercury. Most of the remaining pressure is due to nitrogen.

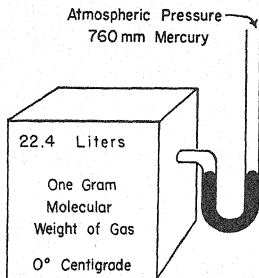


Figure 2-6. Diagram illustrating that one gram molecular weight of a gas confined in a space of 22.4 liters at a temperature of $0^{\circ}\text{C}.$ exerts a pressure of 760 mm. of mercury.

The mercury, shown in black, is in a U-tube. The level of the mercury on the left is shown to be the same as the level on the right because the pressure exerted by the confined gas is 760 mm. of mercury, and this is exactly balanced against the atmospheric pressure of 760 mm. of mercury.

Tension and volumes per cent of a gas in a liquid. When a gas is brought in contact with the surface of a liquid, molecules of the gas enter the liquid; likewise, molecules of gas pass from the liquid through the surface film into the gas above. The number of molecules entering the liquid per unit of time exceeds the number leaving the liquid until, eventually, an equilibrium is established. When this has occurred, the *tension* of the gas in the liquid is the same as the tension of the gas with which the liquid has equilibrated. Thus, if a liquid equilibrates at sea level with atmospheric air having an oxygen tension of 160 mm. of mercury, the tension of oxygen in the liquid is 160 mm. of mercury. This is true regardless of the actual number of molecules of the gas dissolved in the liquid. When a fluid is exposed to a mixture of gases, in accord with the Dalton-Henry law, it will absorb as much of each gas as it would have absorbed if exposed to that tension of each gas separately.

The amount of gas, i.e., number of molecules, dissolved per unit of liquid at a given partial pressure and temperature is determined not only

by the tension of the gas to which the liquid is exposed, but also by the solubility of the gas in the liquid and by the presence in the liquid of any substance that combines with the gas.

The gas laws relating to volume, pressure, and temperature are stated as follows:

(1) The density of an enclosed gas at constant temperature varies directly with the pressure to which it is subjected (*Boyle's law*).

(2) Equal volumes of gases at the same temperature and pressure contain equal numbers of molecules (*Avogadro's law*). The space occupied by one gram molecular weight of any gas under standard conditions (STP) is called its molecular volume, and is equal to 22.4 liters.

(3) The volume of a gas at a constant pressure varies directly with the temperature (*Charles' law*).

Chapter 3

TRANSPORT THROUGH CELL WALLS

The Cell Membrane

The cell membrane in higher animals is the boundary between the cytoplasm of the cell and the fluid which fills the interstices between cells. The interstitial fluid in turn is separated from the blood plasma by the capillary wall. Interchange of certain substances between the blood plasma and interstitial fluid is occurring constantly through the capillary wall, and interchange between the interstitial fluid and the intracellular fluid occurs through the cell wall. One of the most striking and significant features of the cell membrane is its *selective permeability*. The membrane permits various solutes to pass through readily, while it acts as a barrier to the passage of others, or it may allow solutes to pass more readily in one direction than in the other direction.

The cell membrane allows water to pass freely; some dissolved substances pass more or less readily, while other dissolved substances pass through the membrane with difficulty or not at all. The properties of a membrane that make it permeable to some solutes and impermeable to others are not entirely clear. In some cases the size of the molecule evidently plays a part, while in other cases the solubility of the substance in the membrane appears to be a factor. The semipermeability of the cell membrane and of the capillary wall is important in influencing the distribution of solutes and fluids between *blood plasma*, *interstitial fluid*, and *intracellular fluid*. The composition of these three "fluid compartments" shows characteristic differences. Also, the semipermeability of the membrane is concerned with the development of a difference in the electrical charge on the inside and on the outside of the membrane of nerve and muscle fibers. In disease, the cell membrane shows considerable changes in permeability, and some substances apparently alter physiological

processes largely through their influences upon the permeability of the cell membrane.

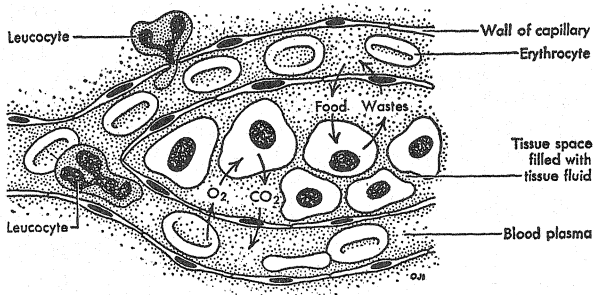


Figure 3-1. Diagram showing tissue, or interstitial, fluid as the medium between the blood plasma and the body cells.

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Physical Processes

Diffusion. Molecules of a gas or other substances in solution are in constant random motion. According to the *kinetic theory* of gases the molecules are relatively far apart and move rapidly in straight lines until they collide with other molecules and then rebound with such perfect elasticity that there is no loss of motion. The pressure exerted by the gas is caused by the impacts of the molecules. If a certain volume of gas is introduced into a closed space, each molecule of this gas will move until it strikes either another particle or the wall of the container from which it will rebound and then strike another and so on until the molecules of the gas becomes equally distributed throughout the closed space. Likewise, when a soluble compound is placed in water the molecules, as a result of random motion, become equally distributed throughout the water. This process is called *diffusion*. A membrane which is permeable to the molecules of the gas or the solute would serve to retard the rate of the process, but would not prevent an equilibrium from being established. Some of

the substances in the body readily can pass through capillary walls and cell walls, and these substances, consequently, tend to become equally distributed throughout the total body water. Other substances can pass through the capillary wall but cannot pass through the cell membrane; still others cannot pass readily through the capillary wall. This makes possible the considerable differences which are observed in the composition of the fluid compartments.

Filtration. *Filtration* is a physical process involving differences in mechanical pressure on the two sides of a membrane. Particles smaller than the pores of the membrane pass through and larger particles are retained. The rate at which the water passes through, other things being equal, depends upon the *hydrostatic* pressure. This is the pressure exerted at the

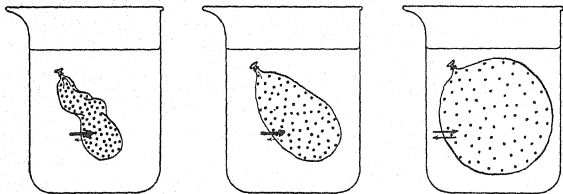


Figure 3-2. Diagram illustrating osmosis.

bottom of a column of liquid, and its amount is directly proportional to the height of the column. By filtration, water and the smaller molecules present in blood plasma are constantly being forced through the capillary wall, while larger molecules and the blood cells are retained in the blood stream.

Osmosis and osmotic pressure. *Osmosis* is a phenomenon which is observed when solutions of unequal concentration are separated by a membrane which is permeable to the solvent and impermeable to the solute. Osmosis, like diffusion, is related to the fact that molecules and ions are in constant motion. Suppose a bag, made of a semipermeable membrane, partly filled with a 10 per cent sugar solution is placed in water. More water molecules will strike the outer surface of the bag per unit of time than will strike the inner surface, since on the inside the sugar particles will interfere; therefore, more water molecules will enter the bag than will leave it. The sugar molecules which strike the inner

surface of the bag cannot pass through. The end result is that the volume of water in the bag will be increased; and, since the total number of sugar molecules contained in the bag is unchanged, the sugar concentration will be decreased. Water will continue to enter the bag until a certain amount of pressure develops within it. The activity of the water within the bag is increased under pressure so that the number of particles striking the wall per unit of time becomes equal to the number striking

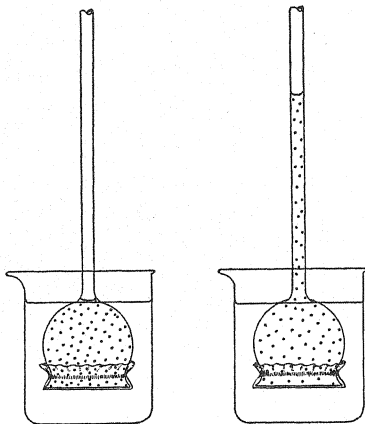


Figure 3-3. Thistle-tube osmometer.

the outside, even though the concentration on the inside is less. Thus, an equilibrium is established at a pressure in the bag which is related to the concentration of the solution. The osmotic pressure of a solution can be illustrated and measured simply as follows. The solution is put in a thistle tube having tied across it a membrane which is impermeable to the solute, and the tube is immersed in water so that the level of the water is at the level of the liquid in the thistle tube. The level of the liquid in the tube will rise slowly until a specific level is reached, this being higher the greater the initial concentration of the solution in the thistle tube. The distance from the top of the column to the level of the liquid in the beaker is a measure of the osmotic pressure. This may be expressed in centimeters

of water or in millimeters of mercury. This figure indicates the amount that the hydrostatic pressure on the upper side of the membrane exceeds that on the lower side of the membrane. It is apparent that the solution in the thistle tube draws water in and upward against the force of gravity; hence *work*, measurable in terms of *weight lifted through distance*, is performed. To understand osmotic pressure it is important to recognize that the pressure developed depends upon the *number of particles* in solution and not upon their size or weight.

Osmotic pressure may be potential rather than actual, and one may calculate the osmotic pressure that a solution is capable of exerting. The term osmotic pressure or osmotic tension is used, according to W. M. Bayliss, to refer to the "properties of solutions conferred upon them by the kinetic energy of their solutes."

Solutions containing the same number of particles per unit volume and hence capable of exerting the same osmotic pressure when separated from water by a membrane impermeable to the solute are *isosmotic*. A solution in which body cells may be placed without alteration of the volume of the cells is said to be *isotonic*; solutions of lower concentration are *hypotonic* and those of higher concentration are *hypertonic*. A 0.9 per cent NaCl solution is isotonic with body cells, and a 5 per cent glucose solution is approximately isotonic. Since the glucose molecule is heavy and does not ionize, it requires 5 gm. of glucose per 100 ml. of solution to yield as many particles as 0.9 gm. of NaCl per 100 ml. of solution. Nutrient solutions which are used for studying the functioning of isolated living cells or tissues must be approximately isotonic.

When a red blood cell, or erythrocyte, is placed in a hypotonic solution, water will enter the cell, causing it to swell, and the increased pressure may disrupt the red cell stroma. Under these conditions the hemoglobin is lost from the red blood cell and becomes distributed throughout the solution. This is called *hemolysis*. That this change has occurred is known from the fact that the solution changes from an opalescent red color to a transparent cherry red. When a red blood cell is placed in a hypertonic solution, water passes from the cell, causing it to shrink, and the cell wall becomes wrinkled or *crenated*. This change can be observed under the microscope.

Reduction in the volume of plant cells is more obvious than in animal cells since in the former the plasma membrane is drawn away from the rigid cellulose wall which is of a fixed size. For example, when the aquatic plant, *elodea*, is in water, osmosis favors the entrance of water into the

cells and keeps them turgid. The plasma membrane is in contact with the cellulose wall which prevents the cell contents from expanding any more and there is a positive pressure within the cell. If a leaf of elodea is placed in a hypertonic solution, water is drawn out of the cell; the cell shrinks and assumes a globular shape as the plasma membrane draws away from the cellulose wall. This process in plant cells is known as *plasmolysis*.

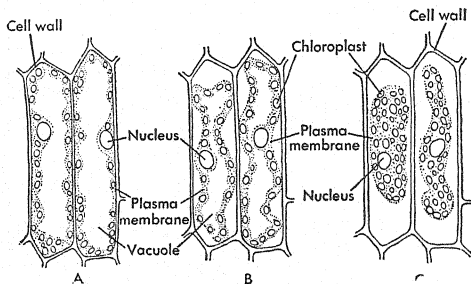


Figure 3-4. Plasmolysis of cells of Elodea.

A. Before adding salt solution. B. Beginning of effect after adding salt solution. C. Completion of effect. (Reproduced by permission from Mavor, *General Biology*. Copyright, 1952, by The Macmillan Company.)

Absorption and Secretion

The physical laws of diffusion, filtration, and osmosis satisfactorily explain the movement of materials through body fluids and cell walls, but in the processes of *absorption* and *secretion* enzymatically controlled chemical reactions are involved in the transport of substances by cells.

The most striking examples of absorption occur in the alimentary canal where the small intestine is the principal organ concerned. The end products of digestion of organic foodstuffs (hexoses, amino acids, glycerol, and fatty acids) diffuse through the cell wall of the intestinal epithelium.

Secretion is concerned with the transfer of substances out of the cell. The material usually is secreted into the lumen of a duct or into the interstitial fluid and thence into the blood stream. Glands of the latter type which secrete products which must be carried to their sites of action by

the blood stream are called ductless, or *endocrine*, glands, and the products of such glands are known as *hormones*. The glands which secrete into ducts are called *exocrine* glands.

Secretion involves three somewhat distinct phases which in some secretory cells are associated with distinct morphological changes. The phases are (1) synthesis of the material to be secreted, (2) accumulation of the material into more or less distinct aggregates, and (3) liberation of the

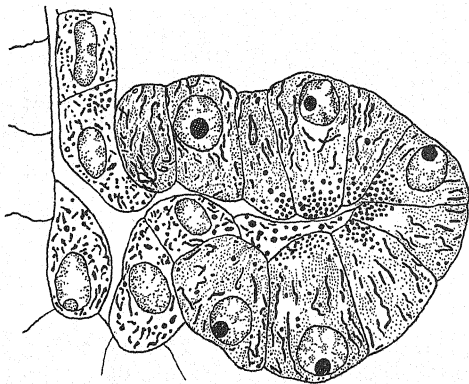


Figure 3-5. Section of secretory cells in the pancreas.

Round secretion granules are shown accumulated at the apices of the cells near the lumen into which the secretion is liberated. (By permission from original of Figure 14, R. R. Bensley, copyright, 1912, by *Am. J. Anat.*, 12: 297.)

substances from the cells. In subsequent sections attention will be given to the mechanisms controlling the production of secretion and its liberation from individual glands.

The products which glandular cells synthesize for secretion are more or less complex. In many of the glandular cells the secretion accumulates in definite bodies called *secretion granules*. These are present in greatest numbers when, for a time, there has been no transfer of material from the cell. When the cell has been actively secreting for a prolonged period the secretion granules may disappear; thus, cytological evidence concerning whether or not the cell has been secreting may be obtained.

Chapter 4

CHARACTERISTICS OF TISSUES

The tissues of the body ordinarily are divided into four major groups: *epithelium*, *connective tissue*, *muscular tissue*, and *nervous tissue*.

Epithelium

Epithelium consists of relatively undifferentiated cells which lay down little or no intercellular substance. Epithelium forms the covering of the surface of the body and the lining of the tubular and globular organs which have connections with the body surface. It includes the secretory cells in both endocrine and exocrine glands, since these originate from surfaces which are covered with epithelium.

On the basis of shape, there are three principal types of epithelial cells: squamous, cuboidal, and columnar.

Squamous (scalelike) cells are thin with more or less irregularly outlined edges. These cells are found, in layers or strata, covering the body surface and lining the mouth and esophagus. Scrapings from the mouth contain large numbers of squamous cells. They are constantly being sloughed off and replaced from the deeper layers.

In *cuboidal* epithelium the height and width of the cells are similar in a section made perpendicular to the surface. When sectioned parallel to the surface they are polygonal. These cells line some of the internal surfaces and are found in many of the glands.

In *columnar* epithelium the height of the cell greatly exceeds its width. This kind of cell is found lining the stomach, small intestine, and colon; a pseudostratified type lines the upper portion of the respiratory passages.

Development of glands. Most of the glands are derived from epithelial layers. At early stages in the growth of the organism a simple tube buds off from the flat layer of cells. Subsequent development varies with the

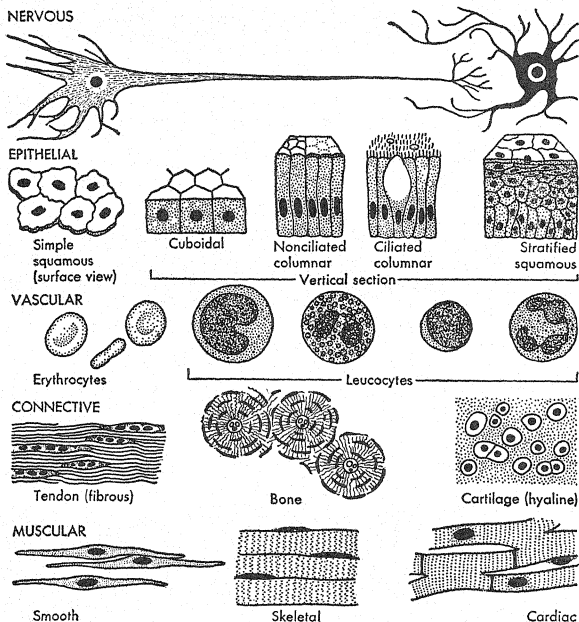


Figure 4-1. The principal types of tissues.

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different glands; some branch and rebranch to become quite complex. The stages of development of a compound gland are illustrated in Figure 4-2. In the case of the ductless glands the connection with the surface from which the gland originated is lost.

Connective Tissue

Connective tissue includes (1) the blood cells and their precursors, (2) connective tissue proper, (3) cartilage, and (4) bone.

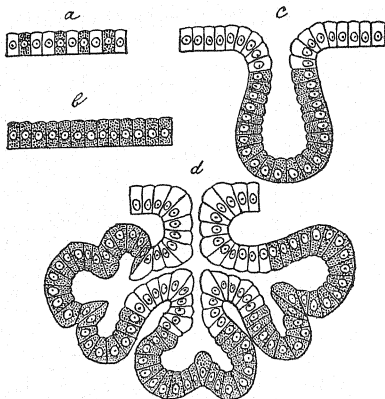


Figure 4-2. Stages in the development of a gland from a layer of epithelial cells. (Reproduced by permission from Maximow and Bloom, *A Textbook of Histology*, copyright, 1948, by W. B. Saunders Co.)

Blood cells. The various types of blood cells are illustrated in Figure 4-3. Their structure, life cycles, and functions will be considered later (pages 177-183). These cells develop in the red bone marrow and lymphatic tissue, through characteristic stages, from one or two types of

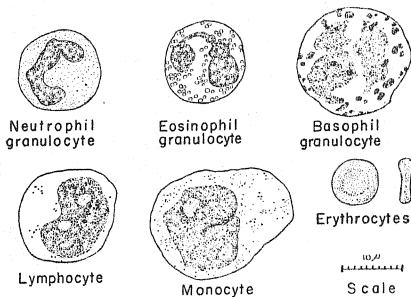


Figure 4-3. Distinguishing structural characteristics of the different types of cells normally found in human blood.

relatively undifferentiated parent cells. The cells normally are liberated into the blood stream only when they reach the mature form; however, in disease, immature forms appear in the circulating blood.

Connective tissue proper. Connective tissue proper is characterized by the presence of intercellular substance containing fibers. The following types are distinguished on the basis of structural features.

Loose connective tissue. This tissue is a whitish sticky material which fills out spaces between organs, thus giving them support and helping to hold them in place. It is easily ripped apart and contains potential spaces. Its main mass is formed of intercellular substance consisting of collagenous fibers, elastic fibers, and amorphous ground substance. The collagenous fibers are flexible, coarse, strong, and resistant to stretch, and are present in large numbers. The elastic fibers are sparsely distributed thin threads. The amorphous substance is a jelly-like material. Loose connective tissue contains fibroblasts, fat cells, and various types of wandering cells. The fat cell is a connective tissue cell with a special fat-storing function. When these cells accumulate in large numbers they produce adipose tissue.

Dense connective tissue. This tissue contains the same elements as loose connective tissue packed into a dense feltwork. It is found in typical form in the derma of the skin.

The regular connective tissue. This includes tendons, ligaments, and fibrous or lamellated sheaths.

Connective tissue with special properties. This group includes miscellaneous specialized types of connective tissue as follows: mucous connective tissue, elastic tissue, reticular tissue, pigment tissue, and adipose tissue.

Cartilage. In this tissue there is a relatively large amount of solid intercellular substance. Several types are distinguished on the basis of differences in the interstitial substance. *Hyaline* cartilage is found connecting the ventral ends of the ribs with the breast bone and forms the surfaces of bones within joints. It contains a dense network of branching fibers. *Fibrocartilage* is found in the intervertebral disks. The interstitial substance contains thick compact collagenous fibers which run parallel to one another and are separated by narrow channels containing the cells.

Bone. Bone is a connective tissue containing cells which lay down collagenous interstitial material that becomes impregnated with calcium salts. There are two major architectural types of bone, compact and cancellous. *Cancellous* bone consists of interconnecting plates and bars form-

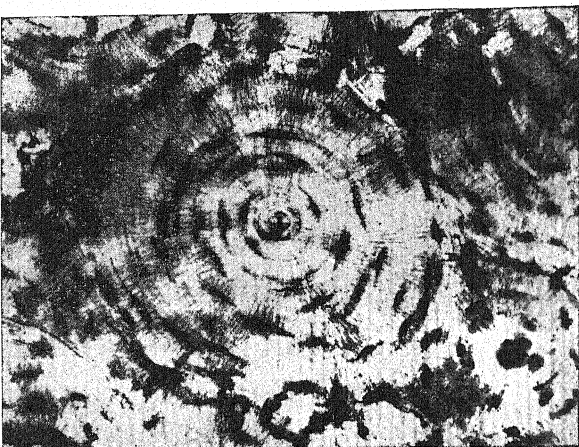


Figure 4-4. Structure of bone.

Above, cross section. Below, longitudinal section. (Reproduced by permission from Weinmann and Sicher, *Bone and Bones*. Copyright, 1947, by C. V. Mosby Co.)

ing a pattern determined mainly by the stresses and strains to which it is subjected. The trabeculae are composed of adjoining layers or lamellae. Lacunae containing osteocytes (bone cells) are found throughout the interstitial substance. The lacunae are connected by means of a network of little canals (*canaliculi*). In *compact* bone the lamellae are regularly arranged. Compact bone is traversed by Haversian canals through which the blood vessels run.

Muscular Tissue

The muscular tissue of higher animals is divided on morphologic and physiologic bases into three types. The structural distinctions will be described briefly here and the functional differences will become apparent in subsequent sections. The types are *striated muscle*, *cardiac muscle*, and *smooth muscle*.

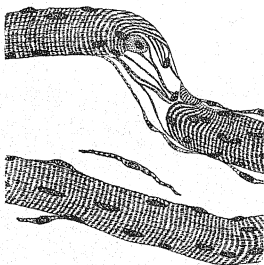


Figure 4-5. Drawing of fibers of skeletal muscle.

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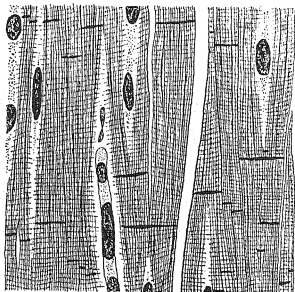


Figure 4-6. Cardiac muscle of the dog.

Longitudinal section.

Striated muscle is sometimes called skeletal muscle, since all of the large muscles acting upon the skeleton to produce movement at the various joints are of this type. A single striated muscle fiber is a long multi-nucleated cell. The fiber consists of numerous longitudinal strands or

fibrils. Each fibril shows, transversely, alternate light and dark bands, which lie opposite each other in the fiber so that transverse striations are prominent. The thin membrane covering the muscle fibers is called the *sarcolemma*.

In the intact muscle the fibers are arranged in bundles of various sizes surrounded by thin sheets of connective tissue, and the direction taken by the bundles of muscle fibers is characteristic for each muscle. For example, in the sartorius muscle, which traverses the full length of the inner aspect of the thigh and aids in crossing the legs "tailor fashion," the fibers run lengthwise of the muscle. In the gastrocnemius (calf-muscle) the fibers, as seen in longitudinal section, are distributed somewhat like the barbs of a feather.

Cardiac muscle is so named because it is found in the heart. It also shows cross striations, but differs from the skeletal form of striated muscle in several respects: The fibers form branching networks, the nucleus is located in the center of the cell instead of on the periphery, and there are heavy cross markings called intercalated disks. The functional importance of the interconnections between cardiac muscle fibers is described in the chapter dealing with the physiology of the heart.

Smooth muscle is also known as plain muscle. It is found in layers in the walls of visceral organs such as the digestive tract, respiratory passages, urinary tract, uterus, and in various other structures. The cells are spindle shaped and contain very fine myofibrils but no cross striations.

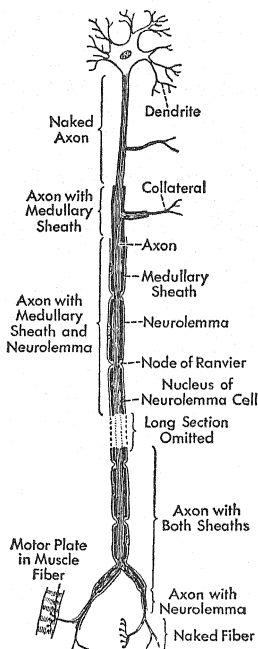


Figure 4-7. Diagram of a motor neuron with sheaths.

(Reproduced by permission from Walter and Sayles, *Biology of the Vertebrates*. Copyright, 1949, by The Macmillan Company.)

Neural Tissue

The conducting cells of the nervous system are known as *neurons*. The nervous system consists of an intricate pattern of neurons bound together and supported by *neuroglial cells*. The neuron consists of a cell body and more or less long branches or processes. The function of the neuron is to conduct impulses which, under physiologic conditions, are received at a specific part of the neuron. The branches which normally conduct impulses toward the cell body are called *dendrites*. Impulses are conducted out from the cell body of the neuron over a branch known as the *axon*. The main parts of a motor neuron, that is, one which conducts impulses to skeletal muscle, are illustrated in Figure 4-7. The processes of some of the neurons are covered by a fatty *myelin sheath*, while others lack this structure; they are called myelinated and unmyelinated fibers respectively.

Other facts concerning structural characteristics of neural tissue are presented in Chapter 6.

Chapter 5

GENERAL ANATOMY AND THE SKELETON

Characteristics of Vertebrates and Mammals

The higher animals are classified under the Phylum Chordata which includes bilaterally symmetrical animals having a dorsally located supporting rod, the *notochord*, and a ventral body cavity through which a digestive tract passes. The notochord is present in the embryonic stage in all chordates. It persists throughout life in some, while in others it is partially or completely replaced by a skull and "backbone."

Vertebrates. The vertebrates are classified as a subphylum of the chordates. The principal classes listed under Subphylum Vertebrata are: fish, amphibia, reptiles, birds, and mammals. All vertebrates are built on the same basic plan. Externally, they are bilaterally symmetrical; the spinal cord is contained within the vertebral column, and there is a well-defined head containing a brain. As in all chordates the body may be envisaged as consisting of a tube-within-a-tube, the inner tube being the digestive tract, the outer being the body wall, and the potential space between the two being the ventral body cavity. The skeleton, nervous system, and musculature show a segmental development; however, the segmentation remains obvious in the adult mammal only in the vertebral column and spinal cord. The vertebrate animal has a closed cardiovascular system consisting of a heart and blood vessels arranged so that blood is pumped from the heart into the arterial tree from which it passes through capillary beds and returns to the heart by the venous system.

Mammals. Mammals are distinguished from all other classes of vertebrates by the presence of *hair* and *mammary glands* and by the separation of the body cavity into thoracic and abdominal portions by a strong musculo-tendinous sheet, the *diaphragm*. Mammals share with birds the distinction of having *constant body temperature*. Birds and mammals also are characterized by having a *four chambered heart*.

Classification. Man belongs to the order of mammals known as *Primates* and the suborder, *Anthropoidea*, which also includes monkeys and apes. The classification of man is summarized as follows:

Animal kingdom

Phylum. *Chordata*

Subphylum. *Vertebrata*

Class. *Mammalia*

Order. *Primates*

Suborder. *Anthropoidea*

Family. *Hominidae*

Genus. *Homo*

Species. *sapiens*

As Le Gros Clark has stated, the *Primates* form a natural group of mammals distinguished from other groups by several prevailing evolutionary tendencies: (1) the preservation of a generalized structure in the limbs, associated with free mobility of the digits and the replacement of claws by flattened nails, (2) elaboration of the visual apparatus and reduction in importance of olfaction, (3) shortening of the snout or muzzle and preservation of a relatively simple pattern of molar teeth, and (4) progressive development of large and complicated brains. In man, the expansion of the brain is greater than in other *Primates* and he shows specialization of the "hind limbs" for supporting the body in the erect position, while the mobility of the foot and toes is less than for other *Primates*.

The members of the *Anthropoidea* are characterized by their somewhat man-like appearance, which "resolves itself on analysis into a few outstanding characters, such as the relatively voluminous and rounded brain case, the flatness of the face, the position of the eyes (which look directly forward and so appear rather close-set), the shrunken appearance of the ears (which do not stand out from the head as in most lower mammals), the alertness and versatility of the facial expression, the mobility of the lips (and especially the upper lip, which is not bound down to the gum as in most lower mammals), the employment for grasping purposes of what is obviously a real hand (and not a forefoot), and the presence of flattened nails on the digits of the hand and foot. These superficial human resemblances of the sub-human members of the *Anthropoidea* are paralleled by many remarkable features of an even more fundamental character, such as are shown in the reproductive func-

tions, the physiology of the brain, or the microscopic structure of certain organs of the body." (From Le Gros Clark, *History of the Primates*.)

Man and the anthropoid apes (of which there are four living types: Gorilla, Chimpanzee, Orangutan, and Gibbon) are grouped into the same superfamily, the Hominoidea. Two other superfamilies include Old World monkeys and New World monkeys.

Organs and Organ Systems

An organ is a more or less discrete structure consisting of tissues arranged according to a definite architectural plan and performing distinct functions. Examples are the heart, liver, stomach, and kidneys. Organs working together to perform related functions are grouped into *organ systems*. However, the multicellular organism operates as a unit and the functions of any cell are intimately related to and dependent upon the functions of most of the organs, hence subdivision into separate organ systems is somewhat arbitrary. Ordinarily, the following organ systems are listed: (1) the *circulatory* system, including the heart, blood vessels, blood, lymphatic vessels, and lymph; (2) the *respiratory* system which includes the lungs and air passages leading to them; (3) the *digestive* system which includes the digestive tract and associated glands which produce the secretions emptying into it; (4) the *excretory* system consisting of the kidneys and channels through which the urine passes to the exterior of the body; (5) the *skeletal* system consisting of the bones and the connective tissue binding them together; (6) the *muscular* system which includes skeletal muscle; (7) the *nervous* system consisting of the central portion, i.e., brain and spinal cord, and the peripheral nerves which carry impulses to and from the central nervous system; and (8) the *reproductive* system consisting of the organs in each sex concerned with the production and transport of the sex cells (ovum and sperm), and in the female, organs concerned with the growth of the fetus and its transport. Frequently, the ductless glands are listed as the *endocrine* system; however, this is not an organ system in the same sense as those previously listed. Hormonal influences are concerned to a greater or lesser degree in the functioning of most of the organ systems. Therefore, it is preferable to consider the functions of some of the endocrine glands in connection with the organ systems most concerned.

General Anatomy

Terminology. The terminology which is used to refer to parts of the surface of the body is shown in Figure 5-1. In Figure 5-2 are illustrated the names of the three planes which are used in anatomical descriptions. Since man stands erect, the portions of the body which are called *dorsal* and *ventral* in other vertebrates also are referred to as *posterior* and *anterior* respectively in man. The *midsagittal* plane is that which divides

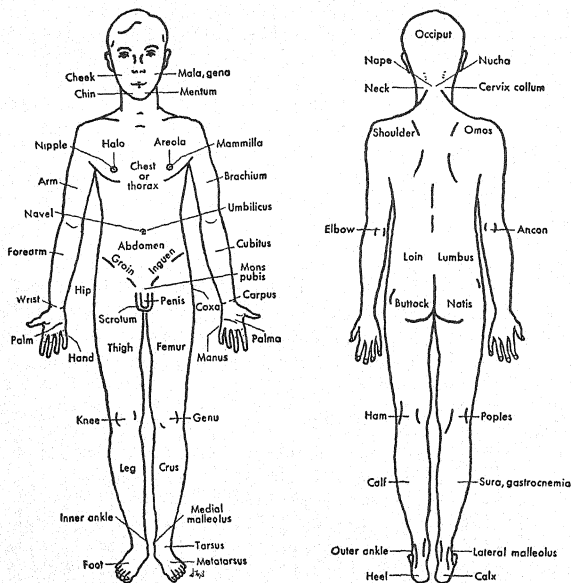


Figure 5-1. Regions of the body.

Latin names are indicated on the right and English names on the left. (Reproduced by permission from Kimber, Gray, Stackpole, and Leavell, *Textbook of Anatomy and Physiology*. Copyright, 1961, by The Macmillan Company.)

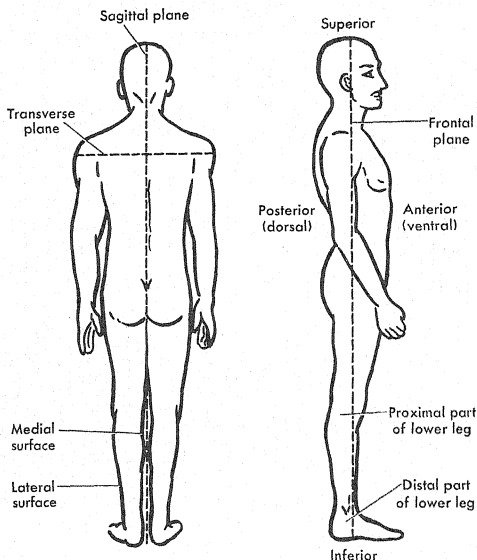


Figure 5-2. Planes of the body.

the body into two symmetrical halves. The *transverse* plane may be at any horizontal level at right angles to the midsagittal plane and the *frontal* plane may be any vertical plane at right angles to the midsagittal plane. Other sagittal planes are parallel to the midsagittal plane. The portion of any part of the body which is toward the center is referred to as *mesial* and that part away from the center is *lateral*. When considering appendages, nerve trunks, blood vessels, etc., the portion toward the middle, or heart or spinal cord as the case may be, is referred to as *proximal*, while the portion toward the periphery is *distal*. For example, if a nerve is sectioned, the end toward the central nervous system can be called the proximal end and the other is the distal end. *Central* and *peripheral* are virtually synonymous with proximal and distal respectively.

Body cavities. The interior of the body generally is described as consisting of two major cavities in which certain organs are located (Figure 5-3). The *dorsal cavity* contains the central nervous system. It consists of the *cranial cavity* which contains the brain, and the *vertebral cavity* in which the spinal cord is located. The *ventral cavity* is the large body cavity which is separated into thoracic and abdominal cavities by the diaphragm. The thoracic cavity is further subdivided into right and left *pleural* cavities by the organs lying in the midportion or mediastinum. The pleural cavities contain the lungs. The *mediastinum*, sometimes called the interpleural cavity, contains the thymus gland, esophagus, part of the trachea and bronchi, and portions of the large blood vessels. The heart (and its surrounding pericardial sac) is contained within the mediastinum.

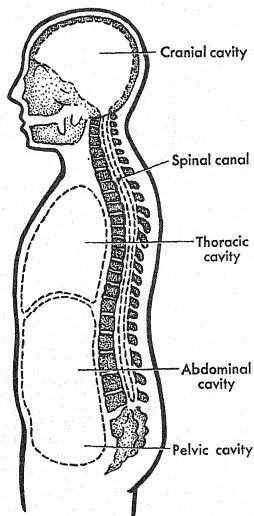


Figure 5-3. The body cavities shown in midsagittal plane.

The abdominal cavity is subdivided for descriptive purposes into upper and lower, or pelvic, portions, although it actually is one large continuous cavity. The liver fills a considerable portion of the upper abdominal cavity on the right. The stomach is in the midpart of the upper abdomen, the spleen is on the left near the diaphragm. The pancreas is seen in the loop formed by the duodenum, the first portion of the small intestine.

The middle and lower parts of the abdominal cavity proper contain the small bowel mesially, and the ascending and descending portions of the colon laterally. The transverse colon is in the upper and posterior part of the abdominal cavity. The pelvic cavity contains the sigmoid colon and rectum, the urinary bladder, and, in the female, the uterus. The kidneys are located in the back of the abdominal cavity against the body wall. The lining of the abdominal cavity is known as the peritoneum. The layer

The middle and lower parts of the abdominal cavity proper contain the small bowel mesially, and the ascending and descending portions of the colon laterally. The transverse colon is in the upper and posterior part of the abdominal cavity. The pelvic cavity contains the sigmoid colon and rectum, the urinary bladder, and, in the female, the uterus. The kidneys are located in the back of the abdominal cavity against the body wall. The lining of the abdominal cavity is known as the peritoneum. The layer

which covers the intestine and continues as the mesentery is the *visceral peritoneum* and that portion which is reflected over the interior of the body wall is the *parietal peritoneum*. The general locations of the organs in the ventral body cavities are shown in Figure 5-4.

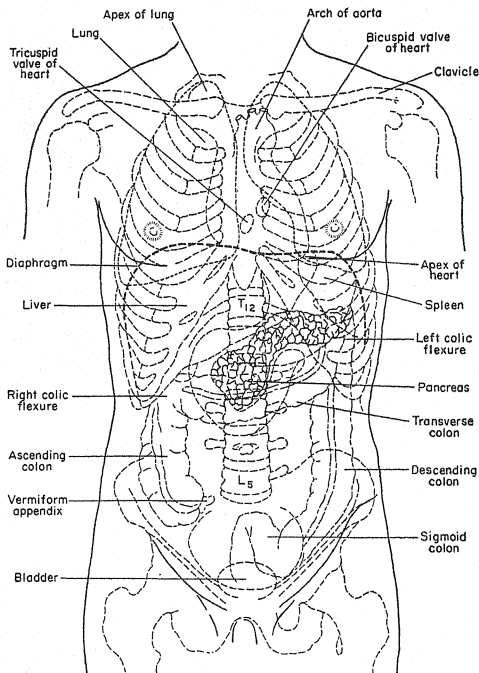


Figure 5-4. Surface projection of the abdominal and thoracic viscera.

Anterior view. (Reproduced by permission from Eyeleshymer and Jones, *Hand Atlas of clinical Anatomy*. Copyright, 1925, by Lea and Febiger.)

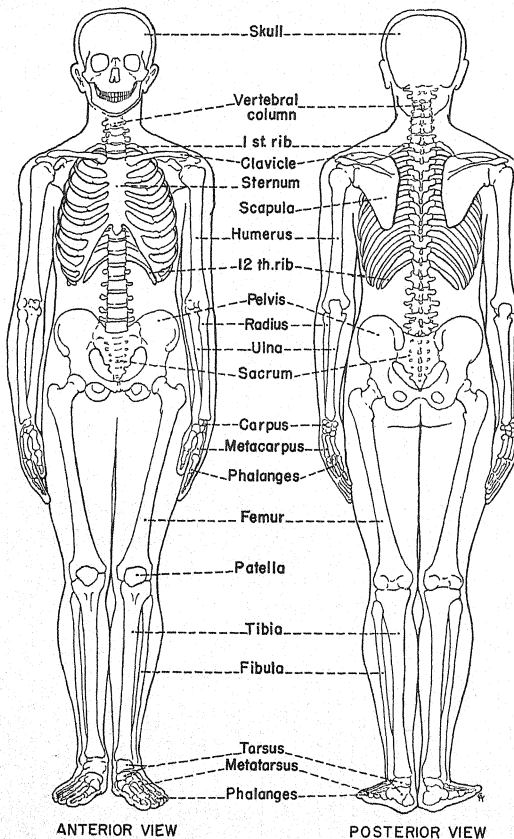


Figure 5-5. The skeleton.

The Skeleton

The skeleton provides support for the body and is the framework upon which the muscles act to produce movement and locomotion. There are two main subdivisions of the skeleton: (1) the *axial* portion includes the skull, vertebral column, and ribs; and (2) the *appendicular* portion includes the two girdles (shoulder and pelvic) and attached bones of the corresponding extremities.

Development of bone. On the basis of shape, bones are classified as long, flat, or irregular. The long bones, such as the femur and humerus (see nomenclature in Figure 5-5) have a characteristic architecture and mode of development.

Flat bones such as those of the skull when completely developed consist of two layers of dense bone connected by a middle layer of spongy bone. These bones form in membrane. The process is known as *intramembranous ossification*. Fibroblasts (cells located in fibrous connective tissue) develop into *osteoblasts* or bone-producing cells. These lay down a gelatinous matrix in which spicules of bone appear. Long thin plates surrounded by osteoblasts develop. Some of the osteoblasts become isolated in individual cavities, the lacunae, and are then called osteocytes or bone cells. The layer of connective tissue surrounding the bone is known as *periosteum*. Its inner aspect is lined with osteoblasts and compact bone is deposited immediately under it as growth proceeds.

Most of the skeleton of the developing embryo appears first as hyaline cartilage. The long bones all develop by *endochondral ossification*. The cartilage is surrounded with perichondrium which changes to periosteum. After the second month of development of the embryo, cartilage gradually is replaced by bone. In the case of long bones the periosteum forms a cylinder of bone at the middle of the shaft. Endochondral bone replaces degenerating cartilage at the center of ossification. The replacement of cartilage with bone proceeds from the center toward the ends of the cartilage. At the same time the cartilage ends continue to grow. A marrow cavity forms within the bone as the ossification centers move toward the ends of the cartilage. At each of the ends, or *epiphyses*, of the structure which is developing into a long bone, additional ossification centers develop. As long as the bone continues to grow the shaft, or *diaphysis*, is separated from the epiphyseal ossification centers by a plate

of cartilage, the *epiphyseal plate* (Figure 5-6). The production of cartilage cells and the formation of new matrix continues on the side of the plate toward the epiphysis while the cartilage on the side toward the diaphysis gradually is replaced by bone. In growing bone the epiphyseal plate is weaker than the other portions and a break or slippage may occur at this region.

Projections from the surfaces of bones are referred to as *condyles* or *tubercles*. The former is a rounded articulating surface such as that found

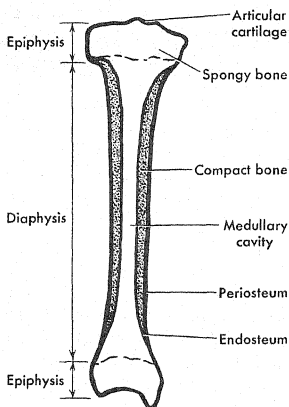


Figure 5-6. Diagram of long bone, longitudinal section.

at the end of a long bone. A tubercle is an elevation which affords attachment for a muscle or ligament.

A *foramen* is a hole in bone through which blood vessels and nerves pass. A hollow cavity within bone, connected with the exterior by small channels, is known as a *sinus*. A depression in the surface of bone is called a *fossa*.

The skull. The bones of the skull include those of the cranium and face. The cranial bones are six in number: (1) frontal, (2) parietal, (3) occipital, (4) temporal, (5) ethmoid, and (6) sphenoid. The first four of these are seen readily in a lateral view of the skull (Figure 5-8). The ethmoid

and sphenoid bones are seen at the base of the skull (Figure 5-9). The parietal and temporal bones are laterally located and are paired. The other four are mesially located and are single.

The bones of the skull are joined by an irregular line of connective tissue at the *sutures*. These are immovable joints. The main sutures are the *coronal* between the frontal and parietal bones, the *sagittal* which extends along the midsagittal line to the posterior fontanel, and the

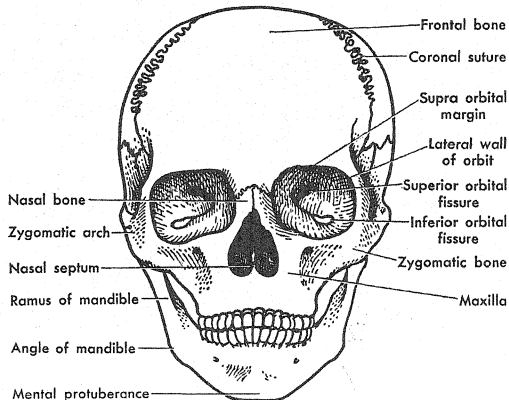


Figure 5-7. Front view of skull.

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lambdoidal which is the boundary between the occipital and parietal bones. In the infant there is a space between the frontal and parietal bones, the *anterior fontanel* (Figure 5-10). Another such space at the end of the sagittal suture between the two parietal bones and the occipital bone is the *posterior fontanel*. The latter is the smaller of the two and closes a few months after birth; the anterior one closes at about 18 months.

The arrangement of the bones of the skull can be learned best by the study of illustrations (Figures 5-7 to 5-9) and by examining a skeleton in the laboratory.

The bones of the face are shown in the anterior and lateral views of the skull (Figures 5-8 and 5-9). These are eight in number: (1) mandible, (2) maxilla, (3) palatine, (4) vomer, (5) zygomatic, (6) lacrimal, (7) nasal, and (8) inferior nasal concha. All of these bones except the mandible and vomer are paired.

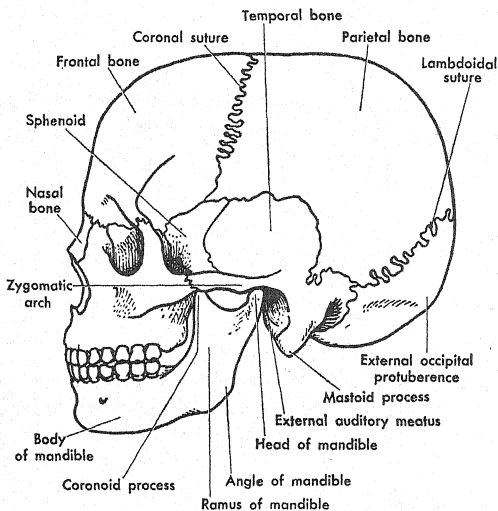


Figure 5-8. Lateral view of skull.

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The nasal cavity and nasopharynx are surrounded by sinuses which open into these cavities by small channels. These are the frontal, ethmoid, sphenoid, and maxillary sinuses which are contained in the corresponding bones. The nasal mucous membrane extends into and lines the sinuses. When the mucosa becomes thickened as a result of colds or infections the channels may become blocked so that the sinuses have no drainage and become filled with secretions. If infection is present a vicious cycle

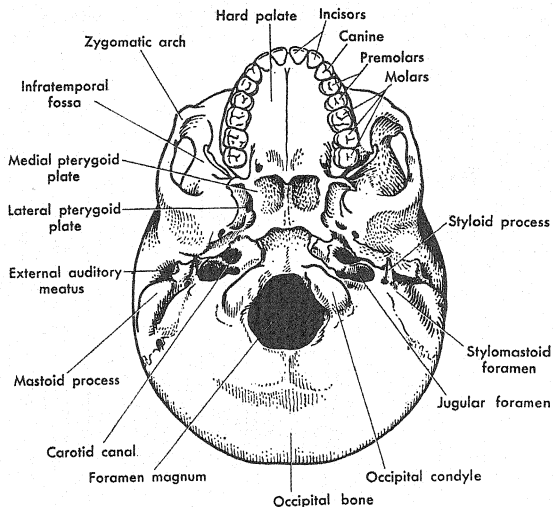


Figure 5-9. View of skull from below.

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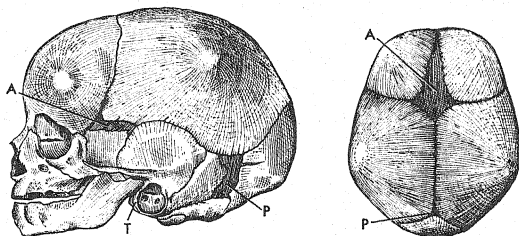


Figure 5-10. Superior (above) and lateral (below) views of skull of infant.

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can become established. Blockage promotes infection and infection promotes blockage. Some of the drugs used in treating sinusitis promote shrinkage of the mucosa and thus cause the channels to open and permit drainage.

Another sinus, the mastoid, is located in the temporal bone and opens into the middle ear. Middle ear infections may extend into it and produce mastoiditis. The sinuses show great variation in size and shape. Casts of the paranasal sinuses are illustrated in Figure 5-11.

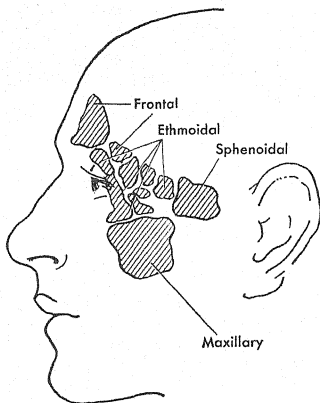


Figure 5-11. Paranasal sinuses.

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Teeth. The dental formula in adult man is

$$\frac{2.1.2.3}{2.1.2.3} \times 2 = 32.$$

This indicates that in both the upper and lower jaws on each side normally, from front to back, there are two *incisors*, one *canine*, two *pre-molars*, and three *molars*. All of these teeth of the adult dentition except molars are preceded in babyhood by temporary or "milk" teeth. The incisors are of spatula-like form. The canine teeth tend to be somewhat

pointed and their prominence varies considerably from one person to another. The crown of the premolar teeth is raised into two little eminences or cusps, hence the name *bicuspid* sometimes is used. The crowns of the molar teeth have a complicated pattern of several cusps.

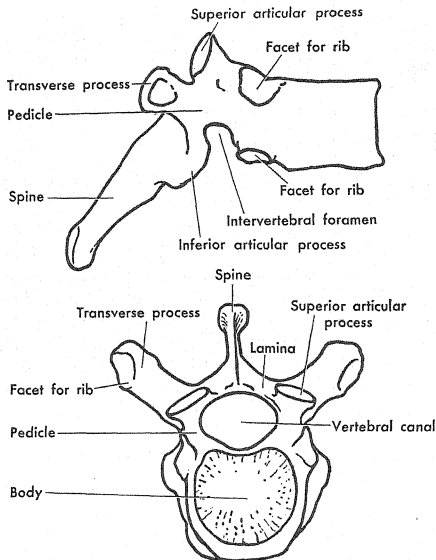


Figure 5-12. A thoracic vertebra from the side and from above.

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The vertebral column. The subdivisions of the vertebral column and the number of vertebrae in each are as follows: cervical, 7; thoracic, 12; lumbar, 5; sacral, 5; coccygeal, 4. The total number of segments is 33, but the last 4 are fused into a single bone, the coccyx, and the sacral 5 are fused to form the sacrum.

The individual vertebra (Figure 5-12) consists of a body, or centrum,

and an arch which forms the vertebral foramen through which the spinal cord passes. There is a transverse process on each side and a spinous process posteriorly. These processes afford attachment for deep muscles of the back. The articular surfaces which make contact between the vertebrae are covered with cartilage. Between each centrum there is a disc of tough connective tissue, the intervertebral disc. This has a center which is somewhat less tough than the periphery and sometimes the disc becomes ruptured or herniated so that it presses against the spinal cord or nerve roots. This produces a characteristic complex of signs and symptoms which may not be relieved unless the herniated portion of the disc is removed surgically.

The first and second cervical vertebrae, *atlas* and *axis* respectively, are specialized to permit a considerably greater degree of movement than occurs at the other intervertebral joints. The body of the atlas is not well-developed and there are large smooth surfaces which articulate with the condyles of the occipital bone. Thus, considerable rotation and flexion and extension are possible at this joint. A characteristic feature of the axis is the odontoid (tooth-like) process, which projects up through the part of the atlas where the body of the atlas would be if this part were well-developed, and provides a pivot on which the atlas can turn.

The thorax. The thorax is composed of the thoracic vertebrae, the ribs, costal cartilages, and sternum. This forms a bony cage which affords protection to the heart and lungs and which can be expanded through muscular action to cause movement of air into the lungs.

There are twelve pairs of ribs. The first 7, or true ribs, attach directly to the sternum through cartilaginous portions. The 8th, 9th, and 10th attach indirectly to the sternum by cartilages which join each other. The 11th and 12th, or floating ribs, are attached only to the vertebral column. The sternum, or breastbone, consists, from above downward, of manubrium, body, and xiphoid process. The clavicle and first pair of ribs articulate with the manubrium. The second pair of ribs attach partly to the manubrium and partly to the body of the sternum.

Shoulder girdle and appendages. In most vertebrates the two pairs of limbs function as pillars for the support of the body. In man, although the arms and especially the hands have become modified for performance of skilled movements, the same basic skeletal plan is found in the arms and legs (Figure 5-13). In each case there is a girdle of bones with which a single bone in the upper arm (humerus) or upper part of the leg (femur) is joined. In the distal portion of the arm there are two

bones; the radius, which is on the side toward the thumb, and the ulna. In the distal part of the leg the tibia is the larger bone and the fibula is the smaller. The carpal bones in the wrist are homologous with the tarsal bones of the foot. Metacarpals of the hand are comparable to metatarsals of the foot, and the bones of the fingers and toes are the phalanges.

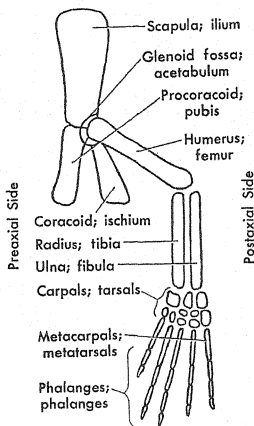


Figure 5-13. Diagram showing the homologies of vertebrate appendages. In each label the first named element is that of the anterior appendage, and the second named is that of the posterior appendage.

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The pelvic girdle and appendages. The homologies of the shoulder girdle and pelvic girdle are not quite so apparent. The pelvic (innominate) bone is formed by the fusion of 3 bones, the ilium, ischium, and pubis, shown in Figure 5-15. In the shoulder girdle the scapula corresponds to the ilium, the coracoid process which is the most prominent projection on the superior edge of the scapula is homologous with the ischium, and the clavicle (procoracoid) corresponds to the pubis.

The bones of the foot form flexible arches. One of these, known as the medial *longitudinal* arch, extends from the ball of the foot to the heel. The lateral longitudinal arch comprises the calcaneum, cuboid, and lateral two metatarsal bones. The transverse arch extends across the foot from the ball to the lateral side. It is located at the junction of the metatarsal bones with the phalanges and also is known as the *metatarsal* arch. Breakdown of the medial longitudinal arch is one of the causes of flat

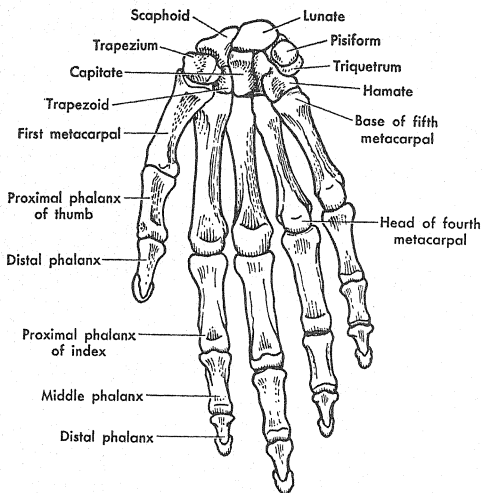


Figure 5-14. Bones of right wrist and hand viewed from palmar side.

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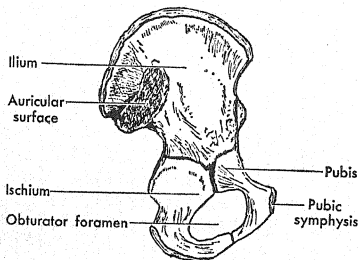


Figure 5-15. Innominate bone from medial side.

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feet. Weakening of the transverse arch may result in an increase in the amount of weight bearing on the second metatarsal and the development of calluses under the peripheral portion of this bone. Also, severe pain in the foot is a common complication of breakdown of the transverse arch. In the greater proportion of the population the first toe is the longest, but in a considerable number of persons, as shown in Figure 5-16,

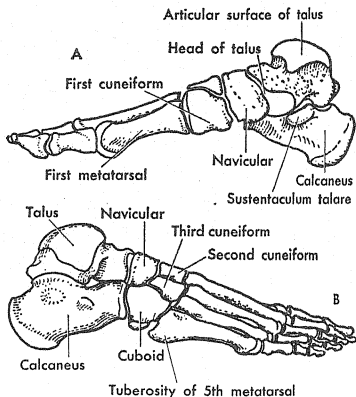


Figure 5-16. Bones of right ankle and foot viewed from above.

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the second toe is the longest. The latter type of configuration is less satisfactory than the former in that the incidence of foot trouble, due to difficulties in the transverse arch, is more common.

Joints. The principal types of joints, classified in the order of increasing mobility, are sutures, synchondroses, symphyses, and diarthroses. (The singular of each of the last three words ends in *is*.) *Sutures* are exemplified by the joints in the skull. The serrated margins of the bones are held together tightly by a thin layer of connective tissue. *Synchondroses* are exemplified by the connections between the ribs and the sternum where bone ends are held together by cartilage. In *symphyses* the bone ends are covered with cartilage and are separated by a disc of

cartilage, the latter being joined to the cartilage on the ends of the bones by means of fibrous tissue. Examples are (1) the joints between the vertebral bodies and (2) the symphysis pubis. The *diarthrosis* is the most complex and most movable type of joint. The principal structural features are shown in Figure 5-17. The two (or more) bones are united by an encircling band of fibrous tissue which is the *joint capsule*. This capsule is lined with a *synovial membrane* which is involved in the production of the colorless viscous synovial fluid. The ends of the bones are covered with cartilage, and the contacting surfaces conform to each other in shape

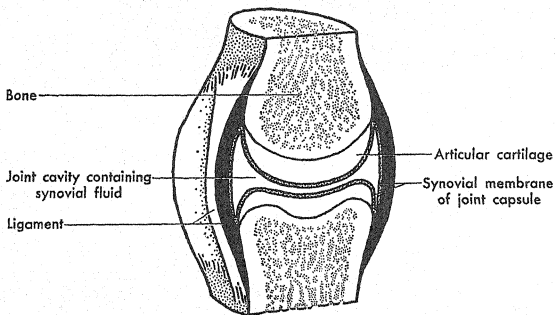


Figure 5-17. Diagram of a diarthrotic joint.

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and are quite smooth. Such joints usually are freely movable. Examples are the shoulder joint and the knee joint. The freely movable diarthroses usually are surrounded by strong ligaments which prevent dislocation.

On the basis of the type of motion which is possible at joints, they are classified as *ball and socket* (EXAMPLE: shoulder), *saddle* (EXAMPLE: carpal-metacarpal joint in the thumb), *hinge* (EXAMPLE: knee joint), *pivot* (EXAMPLE: articulation between the atlas and axis), etc.

In some regions of the body where a great deal of friction occurs in tissues overlying the joints there are sacs or *bursae*, filled with synovial fluid. Most of the long tendons are surrounded with bursal sacs. Inflammation in joints is *arthritis* and in bursae is *bursitis*.

Actions of muscles at joints. Movement at joints usually is accomplished by the action of appropriately attached muscles. At the main hinge joints two motions are possible, straightening and bending. The former is called *extension* and the latter *flexion*. The muscle which produces a given motion may be called the agonist, while that which opposes this action is the antagonist. These muscles are controlled by the nervous

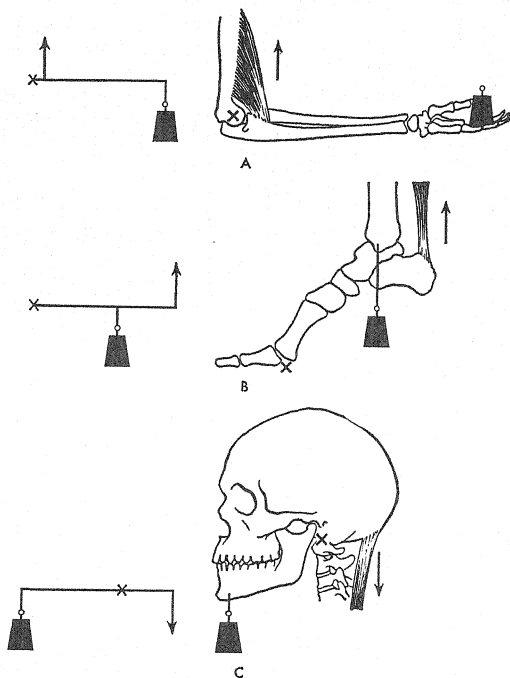


Figure 5-18. The three classes of levers and examples of them in the body.

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system in such a way that when the agonist is caused to contract to produce a certain motion the antagonists undergo decreased activity.

When a muscle acts to produce motion at a joint, commonly the part to which one end is fixed shows little movement, while the other end and affixed bone show considerable movement. The former attachment is known as the *origin* of the muscle and the latter attachment is the *insertion*. In the limbs the origin is usually centrally located.

Movement of a limb in a direction away from the midsagittal plane is known as *abduction* (*ab* = from), and the opposite motion is *adduction* (*ad* = to). *Circumduction* is movement in which the end of the part describes a circle. *Rotation* is turning on an axis, as when the head is turned to the right or left. Rotating the hand to bring the palm upward is *supination* and the rotation in the opposite direction to place the palm downward is *pronation*. *Inversion* and *eversion* of the foot are forms of abduction and adduction respectively.

The leverage at a given joint can be listed under one or the other of three types which are described in physics textbooks. These are illustrated in Figure 5-18.

Chapter 6

GENERAL ORGANIZATION OF THE NERVOUS SYSTEM

Skeletal muscle normally contracts only in response to impulses reaching it by its nerve supply. The muscular, skeletal, and nervous systems may be thought of as functioning essentially as a unit in the maintenance of the position of the body and in determining movement.

In vertebrates the nervous system is composed of a central portion, the brain and spinal cord, and the paired peripheral nerves (Figure 6-1). The nerves contain *afferent* fibers which conduct impulses from sense organs, or *receptors*, to the central nervous system and *efferent* fibers which conduct impulses out to *effector* organs which are capable of responding. Thus, the function of the central nervous system is to receive messages from the parts of the body and from the outside world and, on the basis of this information, to send impulses out over the efferent nerves to produce appropriate patterns of response. Some of the responses to certain types of stimuli involve relatively simple connections in the central nervous system and are immediate and stereotyped, namely, *reflex*. The simpler reflex responses are not acted on by other afferent influences except those occurring simultaneously or only a short time previously.

The Spinal Cord

The spinal cord is a segmented structure and some of its functions are segmental in the sense that afferent impulses may enter at a given segment and evoke impulses in the efferent fibers leaving this segment. Such reflex responses still may be elicited if the spinal cord has been transected both above and below the portion which is concerned, although, as will

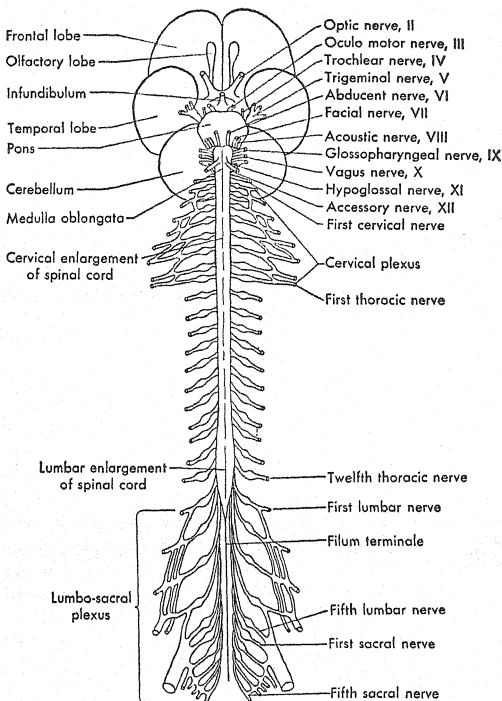


Figure 6-1. Diagram of ventral view of the central nervous system and the origins of the cranial and spinal nerves.

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be considered later, the degree of response usually is somewhat altered when the spinal cord is cut. At any given portion of the spinal cord three types of pathways are found: (1) connections for those reflexes which have their "centers" within that portion, (2) fibers which conduct im-

pulses up to the more cephalad portions of the central nervous system (ascending pathways), and (3) fibers which conduct impulses down to more caudal parts of the spinal cord (descending pathways). Hence if the spinal cord is cut at a given level no afferent impulses can get to the brain from the part of the body innervated by fibers entering the cord below this level, and no descending impulses can reach the neurons which supply skeletal muscle in the part innervated by the nerves which emerge from below the level of the lesion.

Structure of spinal cord. The spinal cord occupies the upper two-thirds of the vertebral canal. It consists of 31 segments each having connected with it a pair of spinal nerves (cervical, 8; thoracic, 12; lumbar, 5; sacral, 5; and coccygeal, 1).

The spinal cord extends from the *foramen magnum* at the base of the skull to the level of the disc between the first two lumbar vertebrae. The disparity in the length of the spinal cord and the vertebral column is related to the fact that the latter grows more in length after the third month of fetal life. The nerve roots arising from the lumbar and sacral regions pass down some distance within the vertebral canal to reach the points of exit, thus forming a bundle of roots called the *cauda equina* (horse tail).

In Figure 6-2 a cross section of the spinal cord with the connected pair of spinal nerves is shown diagrammatically. The outer portion is white and in the center gray matter is present in the general shape of a capital H. The gray matter is composed of cell bodies and their processes. The white matter consists of cross sections of ascending and descending fibers which, for the most part, are surrounded by myelin sheaths. Myelin is white. Cell bodies are concentrated in the limbs of the H, and the cross bar consists mainly of nerve fibers which pass from cell bodies in the dorsal part of the H on one side to form synapses with cell bodies in the lateral or ventral portion of the H on the opposite side.

The posterior limb of the H is known as the *posterior column* of gray matter, the anterior limb is the *anterior column* of gray matter. The bar is the *gray commissure* or *central gray*. The columns of gray matter divide the white matter of the cord into *anterior*, *lateral*, and *posterior funiculi*. The size and shape of the spinal cord and the relative proportion of the cross section area occupied by the different columns and funiculi vary at the different levels. The space occupied by ascending and descending tracts is greater at the higher levels, while the parts of the cord which give rise to efferent fibers supplying the limb muscles have large anterior

gray columns, since this is the region in which the cell bodies of the motor neurons are located.

The spinal nerves. The spinal nerves are connected to the cord by two roots, dorsal and ventral, which join to form the nerve on each side. The spinal ganglion found on the dorsal root contains the cell bodies of sensory (afferent) neurons and the fibers which connect with the spinal cord carry impulses in to reach synapses with neurons in the gray matter.

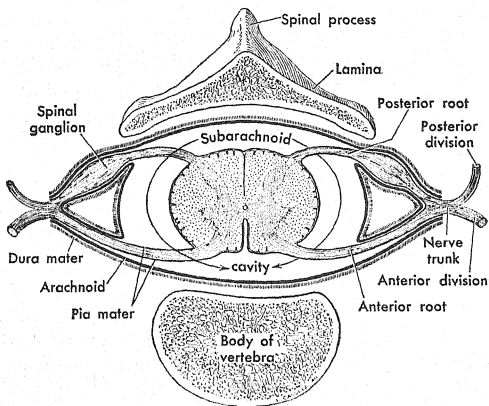


Figure 6-2. Cross section of spinal cord.

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The fibers which are present in the ventral roots are efferent. They are the axons of cell bodies located, for the most part, in the anterior gray column. From the point of fusion of the two roots the spinal nerve contains both afferent and efferent fibers. A few millimeters beyond the point where the nerve is formed it divides into posterior and anterior divisions, each of which also contains both afferent and efferent fibers. In general, the posterior division innervates the muscles of the back and the skin covering them, while the anterior division, which is the larger, innervates the muscles and skin of the extremities and the remaining areas of the

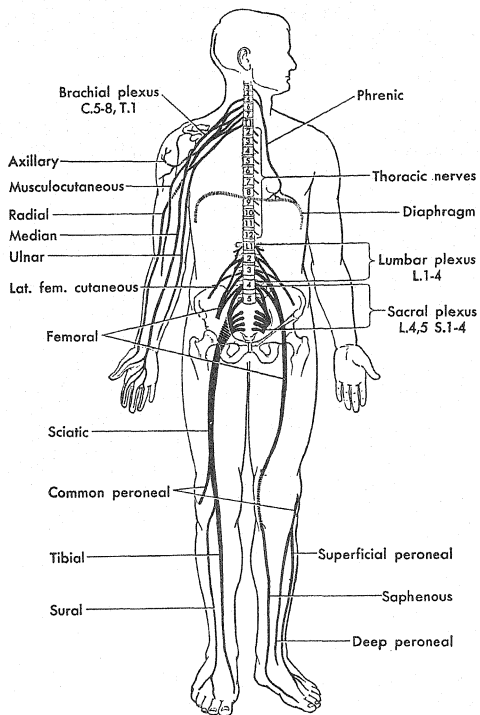


Figure 6-3. The brachial and lumbar plexuses and principal nerves.

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trunk. The distribution of the spinal nerves and names of the main nerves of the body are shown in Figure 6-3.

Tracts in the spinal cord. The tracts of the cord are located in certain areas as seen in cross section (Figure 6-4). The pathways for the

cutaneous senses (cold, warmth, pain, and touch) follow a definite course and are grouped in bundles occupying specific portions of the cord. Pathways which conduct impulses from receptors in skeletal muscle tendons and joints are known as proprioceptive. *Proprioception* is the sense by which one is aware of the position of the body. Afferent paths for this sense occupy much of the dorsal and lateral portions of the spinal cord as shown in Figure 6-4. Some of these tracts convey impulses to the cerebellum and others conduct to portions of the cerebrum.

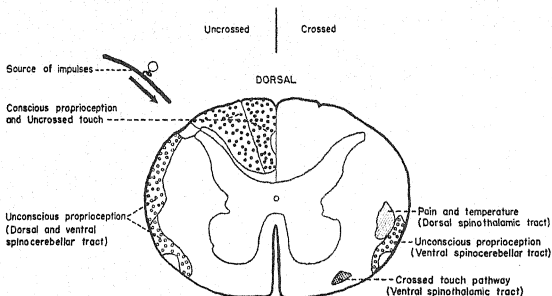


Figure 6-4. Cross section of spinal cord (cephalad side) showing location of ascending pathways concerned with conduction of impulses entering by a dorsal root on the left.

(From Youmans' *Basic Medical Physiology*.)

Descending fibers pass from cell bodies of neurons in the cerebral cortex and other parts of the brain down to the vicinity of motor neuron cell bodies in the anterior gray column. These tracts also occupy specific parts of the spinal cord. Further points about the principal tracts will be considered in subsequent chapters dealing with the general senses, posture, and voluntary movement.

Localization of function in the nervous system also is observed in the highest portion, the cerebral cortex. There are sites of input for the general and special senses, known as sensory areas, and well-defined parts of the cortex are concerned directly with the control of skeletal muscular activity. The latter are known as motor areas.

Parts of the Brain

The three major parts of the brain are the *cerebrum*, the *cerebellum*, and the *brain stem*. The brain stem is the modified and expanded anterior extension of the spinal cord. The *cerebral hemispheres* and associated structures, *corpus striatum*, *internal capsule*, and *corpus callosum*, compose what is known as the *forebrain*. This part of the brain is larger and

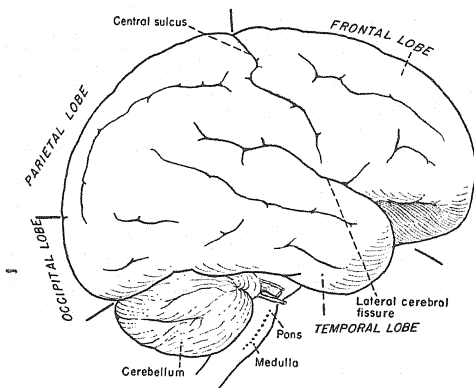


Figure 6-5. Drawing of lateral view of the brain.

Only the more prominent sulci and fissures are shown. These afford a basis for division into lobes.

more highly developed, the higher the animal's place in the phylogenetic scale. The principal parts of the brain as seen in the lateral and sagittal views are labeled in Figures 6-5 and 6-6.

On section, the brain is seen to have an outer covering, or *cortex* (bark), which is gray in color and the deeper portions are white. In general, the white matter in the nervous system is composed largely of axons with their white myelin sheaths, while the gray matter consists mainly of cell bodies of the neurons. In the spinal cord the cell bodies, and hence the gray matter, are centrally located and the outer portion of the cord is composed of white matter.

The surface of the cerebral hemispheres has characteristic folds, or *convolutions*; the convolutions are known as *gyri* and the grooves between them are *sulci*. There are three prominent grooves: the *sylvian fissure*, the *central fissure*, and the *longitudinal fissure*. Each cerebral hemisphere is divided into four lobes: *frontal*, *parietal*, *occipital*, and *temporal*. The frontal lobe is the part lying anterior to the central fissure, the temporal lobe is the portion below the sylvian fissure, the parietal lobe is posterior

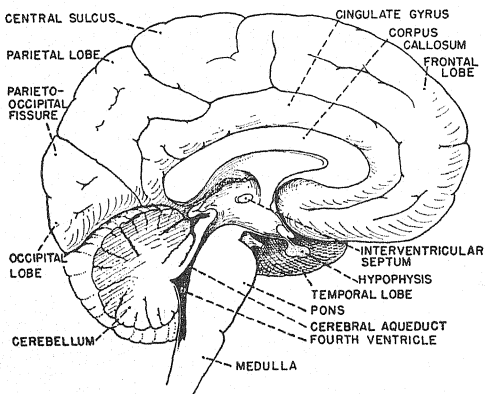


Figure 6-6. Drawing of sagittal section of the brain.

to the frontal lobe, and the occipital lobe is the most posterior part of the cerebrum. The longitudinal fissure separates the right and left halves of the cerebrum.

The longer nerve fibers composing the white matter of the deeper portions of the cerebral hemispheres are divided into three major classes: (1) *projection* fibers passing upward to the cortex from cell bodies in the brain stem and passing downward from the cortex to connect with nuclei in the lower parts of the brain and in the spinal cord, (2) *association* fibers which interconnect portions of the cerebral cortex, (3) *commissural* fibers which pass between the two cerebral hemispheres.

The part of the brain below the forebrain includes the *thalamus*, the

hypothalamus, pineal body, and geniculate bodies. Thalamus means chamber; it is the part of the brain bounding the cavity of the third ventricle. Each cerebral hemisphere contains a ventricle and these together are the lateral ventricles. They contain cerebrospinal fluid and each drains by a foramen of Monro into the third ventricle. The pineal body is at the roof of the third ventricle and the hypothalamus with the attached pituitary gland is at the floor of the third ventricle. The pituitary gland also is known as the hypophysis.

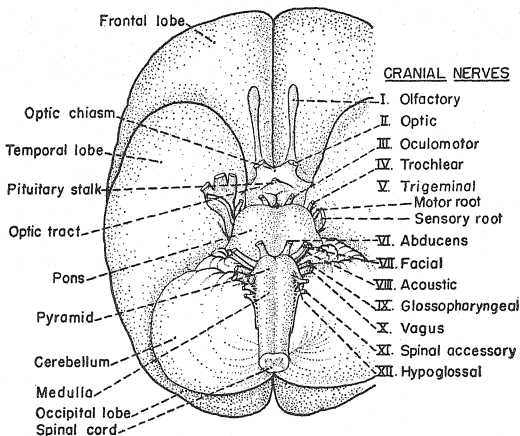


Figure 6-7. Diagram of ventral surface of the brain showing points of origin of the cranial nerves.

There are 12 pairs of cranial nerves all of which are attached to the brain stem except the olfactory nerves which are most anterior. Consecutively, proceeding down from the parts of the brain already listed, the brain stem is composed of *corpora quadrigemina*, *cerebral peduncles*, *pons* with attached cerebellar peduncles, and the *medulla oblongata* which is continuous with the spinal cord. The word, peduncle, comes from a Latin word meaning stem or supporting part. Thus, the cerebral peduncles are the parts of the brain stem which support the cerebrum

and the cerebellar peduncles support the cerebellum. The twelve pairs of cranial nerves are:

- | | |
|-----------------|---------------------------------|
| I. Olfactory | VII. Facial |
| II. Optic | VIII. Auditory (and Vestibular) |
| III. Oculomotor | IX. Glossopharyngeal |
| IV. Trochlear | X. Vagus |
| V. Trigeminal | XI. Spinal Accessory |
| VI. Abducens | XII. Hypoglossal |

Cerebrospinal fluid. The ventricles of the brain, the spinal canal, and the subarachnoid space which lies between the arachnoid layer and the brain and spinal cord, contain a liquid known as cerebrospinal fluid. This fluid serves for support and mechanical protection of the central nervous

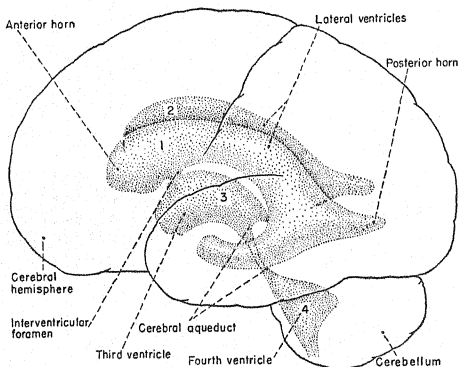


Figure 6-8. Ventricles of the brain.

system and allows for changes in volume of the brain. The pressure within the structures containing cerebrospinal fluid averages around 125 mm. of water. Obstruction of venous drainage from the cranial cavity, as by compressing the jugular veins, causes the pressure of the cerebrospinal fluid to rise sharply.

The cerebrospinal fluid is formed by *choroid* plexuses in the lateral ventricles and in the fourth ventricle. For the most part, its formation is

accomplished by filtration and diffusion. All of the substances present in cerebrospinal fluid are present in the blood plasma; however, there are considerable differences in concentration.

The cerebrospinal fluid flows from the lateral ventricles through the foramina of Monro into the third ventricle and thence through the aqueduct of Sylvius into the fourth ventricle which lies just posterior to the medulla oblongata. The fourth ventricle is continuous with the central canal of the spinal cord, and at each side of the fourth ventricle there is a foramen opening into the subarachnoid space. The fluid flows from the fourth ventricle through these openings and spreads over the whole surface of the brain and spinal cord. Resorption of cerebrospinal fluid occurs through *arachnoid villi* into the superior longitudinal sinus and other dural sinuses which empty into the venous system. In Figure 6-8 the ventricular system of the brain is illustrated.

Chapter 7

STIMULATION AND RESPONSE OF NERVES AND SKELETAL MUSCLE

Some cells possess the property of irritability in a more specific sense than is the case for protoplasm in general. This is true for nerve, muscle, and the secretory cells of glands. Since such tissues comprise the more active parts of most organs and since the activity of many of the organs is controlled through their nerve supply, knowledge of basic facts concerning the physiology of the irritable tissues and of the simpler neural mechanisms such as reflex action is necessary in order to understand the functioning of organs and organ systems.

The cells of nerve, muscle, and glands resemble each other and differ from other cells, for example, those of bone and connective tissue, in that they show an immediate response to an appropriate stimulus. The nerve fiber conducts impulses, the muscle fiber conducts impulses and contracts, and the glandular cell secretes. In some instances the response is visible to the unaided eye, while in other cases special recording devices are necessary to detect it.

Processes Involved in Reflex Action

The different types of problems which are encountered in the study of the irritable tissues become apparent when one considers a reflex such as the knee jerk. If a subject sits on a table with his lower leg swinging free so that it forms approximately a right angle with the thigh, a brisk tap just below the kneecap elicits a sudden contraction of the quadriceps muscle in the upper leg, and the lower leg is momentarily extended at the knee joint. It is appropriate to use the knee-jerk as an example to introduce the study of reflexes because it is accomplished through the simplest kind

of reflex pathway involving the central nervous system. Only two types of neurons are required and only one synapse is interposed in the reflex pathway, hence this is known as a *two-neuron*, or *monosynaptic*, reflex arc. The pathway is diagrammed in Figure 7-1. The figure is a simplification in that a number of afferent neurons and efferent, or motor, neurons are utilized; actually, any one afferent neuron diverges to supply a number of motor neurons and fibers from several afferent neurons converge upon each motor neuron.

The knee-jerk may be described now with reference to the actual structures involved. The blow below the kneecap briefly stretches the tendon of the quadriceps muscle which contains receptors which are activated by

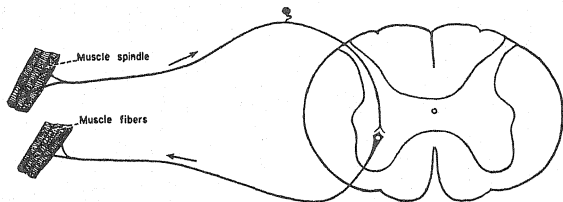


Figure 7-1. Two-neuron reflex arc.

Pathway for the muscle stretch reflex. (From Youmans' *Basic Medical Physiology*.)

the sudden change in tension, and impulses are conducted from the receptors by afferent nerve fibers into the spinal cord to reach the motor neurons. Impulses arriving at synapses with cell bodies of the motor neurons cause impulses to be set up in them, and the impulses are conducted out along the axon to the junction of the efferent nerve with the skeletal muscle fibers. Then impulses are set up at the neuromuscular junctions and are conducted along the muscle fibers. Immediately after passage of the impulse the muscle fibers contract. Thus, the reflex involves, consecutively: (1) activation of a receptor, (2) conduction of impulses in the afferent nerve, (3) transmission of excitation across synapses in the spinal cord, (4) conduction of impulses in the efferent neuron, (5) transmission of excitation at the neuromuscular junction, (6) conduction of the impulses in the muscle fibers, and (7) contraction of the muscle fibers. The main basic processes to be considered, therefore, are excitation, conduction (which basically is similar in all types of nerve fibers and in muscle),

synaptic transmission, neuromuscular transmission, and muscular contraction. These processes, together with elementary physical principles necessary to understand them, will be described next.

Polarization of Membranes

It is a striking characteristic of muscle fibers and nerve fibers that the outside of the fiber is positively charged and the inside is negatively charged. This phenomenon, known as *polarization*, is intimately related to excitation of the fiber and to conduction of impulses. Before considering polarization further, it is necessary to know certain facts concerning the production of electric current.

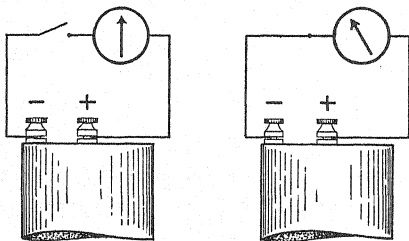


Figure 7-2. Simple electrical circuit.

The two poles of a dry cell battery are shown connected in a circuit with a key and a device for recording current. In A the key is open; in B the key is closed and deflection of the needle indicates flow of current.

A dry cell battery has a positive pole and a negative pole as shown in the diagram, and when these poles are connected in a circuit with a current-recording device, or *galvanometer*, the needle will be deflected from the zero position. The amount of current which flows in the circuit is proportional to the strength of the battery. The amount of current is expressed as *amperes* and the strength of the battery is expressed as *volts*. The other factor which must be known in predicting the amount of current which will flow in any circuit is the *resistance* in the circuit. For example, if iron wire which offers a high resistance is used, less

current will flow, while if copper wire which offers little resistance to flow of current is used, a higher current will be recorded. Thus, *the amount of current (I) which flows in a circuit at a given time is directly proportional to the electromotive force or voltage (E) and inversely proportional to the resistance (R).* This is indicated by the formula.

$$I \text{ (intensity)} = \frac{E \text{ (electromotive force)}}{R \text{ (resistance)}}$$

If one desires to increase the current in a circuit, he may do so either by decreasing the resistance, if this is considerable, or by increasing the voltage.

In the squid, there are giant axons which are large enough so that a needle-like microelectrode, coated with insulating material, can be inserted through the membrane of the axon thus permitting a comparison of the charge in the interior of the fiber with that of the surrounding sea water or with the charge on the outside of the fiber. The inside of the axon is found to be negatively charged.

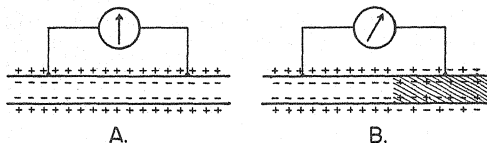


Figure 7-3. Diagram of conditions for recording injury current.

In A an uninjured nerve fiber is shown connected in a circuit with a device for recording current (galvanometer). Both electrodes are placed on the polarized membrane and, since conditions under the two electrodes are identical, no flow of current occurs. In B the right-hand end of the nerve fiber is represented as being injured and the membrane is no longer polarized; the left electrode is in a field which is positive and the right electrode is in a field which is neutral. Since there is a difference in potential at the two sites, current will flow. (From Youmans' *Basic Medical Physiology*.)

Another method for demonstrating that nerve fibers are polarized is to connect in a circuit with a galvanometer two electrodes, one of which is placed on the uninjured end of a nerve and the other on a crushed or otherwise damaged portion of the nerve. The electrode on normal nerve is found to be positive as compared with the electrode on the injured portion of the nerve. The injury has destroyed the semipermeability of the membrane so that the positively and negatively charged particles

become equally distributed on the two sides of the membrane. Since the injured portion of nerve is neutral and the uninjured portion is positive as compared to the injured end, one must conclude that the uninjured portion has a positive charge. The current which is recorded under the conditions just described, illustrated in Figure 7-3, is known as the *injury current*.

Conduction of Impulses

In the intact organism nerve fibers conduct impulses from the receptors which they innervate or are "fired" by impulses arriving at synapses. The direction of conduction of the impulse is away from the site of activation of the neuron, and the neuron is named according to the direction of conduction. *Afferent* nerves conduct impulses from receptors toward the spinal cord or brain; *efferent* neurons conduct impulses out from the central nervous system to the responding tissues or *effectors*. The afferent fibers enter the spinal cord by the dorsal, or posterior, roots, and the efferent fibers leave by the ventral, or anterior, roots. When sections of nerves are removed from the body and drying is prevented, the fibers remain irritable and are still capable of conducting impulses. Such an isolated fiber can be stimulated by artificial means, and it will conduct an impulse in both directions from a site of stimulation whether the fiber is afferent or efferent.

Action currents. When muscle or nerve is stimulated effectively, either by the use of electrical stimulating devices or by other methods, the polarity over a portion of the fiber is reversed. This is illustrated in Figure 7-4,A. Once a section of the fiber undergoes reversal of polarity, local currents are set up which influence the adjacent polarized section on each side in such a way as to cause them to show a similar change; thus, the process moves rapidly along the fiber in each direction from the site of stimulation. In the wake of the impulse the normal polarity of the membrane is rapidly restored. Therefore, shortly after stimulation of the fiber a segment somewhat removed from the locus of the stimulating electrode will be involved, and polarity will have been restored at the site of stimulation. This stage is illustrated in Figure 7-4,B which also shows that at this time a potential difference will exist between the leads to a galvanometer, and a flow of current will be recorded. As the wave passes on to the right, it will lie between the two leads of the galvanometer; the membrane

under both leads will be polarized, hence the needle will return to the perpendicular position. If the major changes in current recorded by the galvanometer are graphed, the type of curve illustrated in Figure 7-5 is obtained. At the time corresponding to A of Figure 7-4 the impulse is between the site of stimulation and the left-hand electrode. At B the impulse is under the left-hand electrode. At C it is between the electrodes, and the length of segment marked C is proportional to the distance between the electrodes. At D the impulse is under the right-hand electrode, and at E it is between this electrode and the end of the fiber. The curve obtained is called a *diphasic action current*.

Another method of recording gives a so-called *monophasic action current*. One lead to the recording device is placed on the uninjured end of a fiber and the other is placed on the injured end as illustrated in Figure 7-6,A. In this case the needle remains deflected under resting conditions and indicates the injury current. When the nerve is stimulated, the needle is deflected toward zero as the impulse comes under the left-hand electrode. The needle returns to its previous position as the impulse passes on to the right and dies out at the junction be-

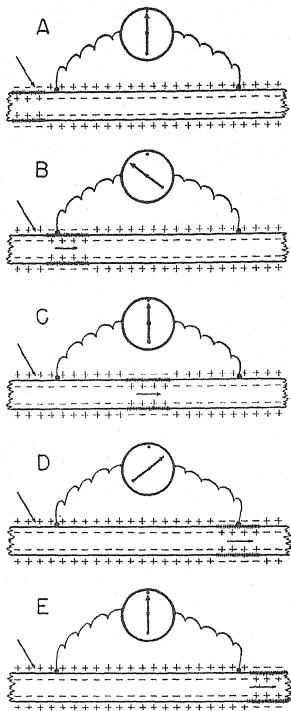


Figure 7-4. Diagram of basis for diphasic action current.

The uninjured nerve fiber is connected in a circuit with a galvanometer. A stimulus is applied at the point indicated by the arrow. The impulse moves along the fiber to the right, and at the site of the impulse the polarity of the membrane is reversed. (From Youmans' *Basic Medical Physiology*.)

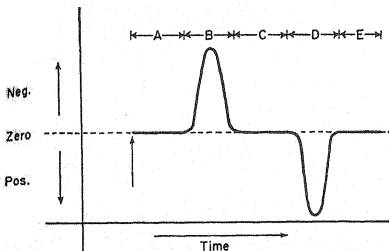


Figure 7-5. Diagram of diphasic action current.

(From Youmans' *Basic Medical Physiology*.)

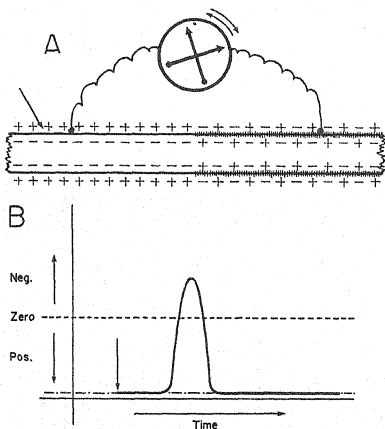


Figure 7-6. A. Method for recording monophasic action current.

Stimulus applied at point indicated by arrow. Needle remains deflected to right by injury current and swings back past the perpendicular as impulse passes under the left electrode.

B. Diagram of monophasic action current.

(From Youmans' *Basic Medical Physiology*.)

tween the uninjured and injured tissue. The curve is graphed in Figure 7-6,B. Since the passage of each nerve impulse or muscle impulse is associated with changes in polarity of the membrane, it is possible to detect when an impulse passes along a fiber.

It is important to remember that the height of the action potential recorded from an intact nerve, which contains a large number of fibers, is determined by the total number of impulses passing under the electrode at the same instant. In other words, the action potentials from the individual nerve fibers are of a specific amplitude and if only one impulse passes under the electrode in one fiber a relatively small deflection will be seen on the oscilloscopic screen, but if impulses pass simultaneously in several fibers, a proportionately larger action potential will be observed.

Mechanism of production of the action potential. The polarization of the cell membrane is related closely to the fact that cations such as K^+ and Na^+ are unequally distributed on the two sides. There is a higher concentration of Na^+ on the outside and of K^+ on the inside. It is now believed that an active process (which involves enzymes and energy consumption) is concerned with keeping Na^+ pumped out of the cell. When this is done the similarly charged K^+ tends to enter and replace the Na^+ . The latter movement is related to the fact that ions carrying similar charges tend to repel each other. It is known that the passage of a nerve impulse is associated with an increase in permeability of the membrane of the axon as indicated by the fact that Na^+ enters the axon and K^+ passes out, and a part of the process of recovery consists of the elimination of the Na^+ which has entered and the return of K^+ which was lost.

Electrical Stimulation

Any influence which tends to depolarize muscle or nerve may serve as a stimulus. The stimulus is said to be *effective* if the depolarizing influence is of sufficient degree over a sufficient length of the fiber so that a propagated impulse is set up. A stimulus weaker than this is *ineffective* (subliminal, subthreshold, or subminimal). Although osmotic, chemical, mechanical, and electrical influences may serve as stimuli, electrical stimuli are used most commonly for artificial stimulation of nerve, muscle, and other irritable tissues because the strength and duration of the stimulus may easily be controlled and may be kept at a level such that the tissue will not be damaged.

The effectiveness of electrical stimulation depends upon (1) the *rate of change* of the current level, (2) the amount of change in *intensity*, and (3) the *duration* of flow of the current. If the current applied is increased very slowly, it will not stimulate even though a high intensity is reached, whereas a quick rise to a relatively low intensity may be effective. There is a *minimum length of time that any current must flow*, in order to be effective. This time, measured in milliseconds, decreases as the current intensity increases. When this value for each of several current strengths is graphed, the curve obtained is called the strength-duration curve.

When a nerve or muscle is stimulated, the strength of stimulus may be increased stepwise from very low levels so that it is ineffective, or submaximal, or maximal, or supramaximal. An ineffective stimulus is one which activates no fibers. A submaximal stimulus is effective for fibers close to the electrode and ineffective for similar fibers farther away. As the current is increased, the more distant fibers also are activated, and finally all fibers are involved. A stimulus that activates all fibers is maximal, and currents of greater strength than this constitute supramaximal stimuli.

A stimulus that is inadequate to set up an impulse is not completely without effect. It causes, for a brief period, a local decrease in threshold, and when several subliminal stimuli are applied sufficiently rapidly, a summation will occur so that finally an impulse may be initiated. Individual fibers of nerve and muscle show what is known as an *all-or-none* reaction; that is, a stimulus either fails to set up an impulse or it causes a full-size impulse. Once the impulse is set up, it has the same characteristics, no matter how it was produced.

Changes in excitability following response. After an impulse has been produced at a given region of a fiber of nerve or muscle, there is a period during which a second impulse cannot be produced at this site regardless of the strength of the stimulus applied. This interval is called the *absolutely refractory period*. Following the absolutely refractory period, the fiber progressively regains its irritability during an interval which is called the *relatively refractory period*. During this time the fiber can be stimulated, but the minimal current required for an effective stimulus is greater than normal. The relatively refractory period is considerably longer than the absolutely refractory period, and the duration of these periods varies with the different irritable tissues; the periods are shortest in nerve fibers of large diameter and are much longer in cardiac muscle.

Velocity of conduction. The *rate of conduction* of impulses varies from one nerve fiber to another. The conduction in the fastest nerve fibers

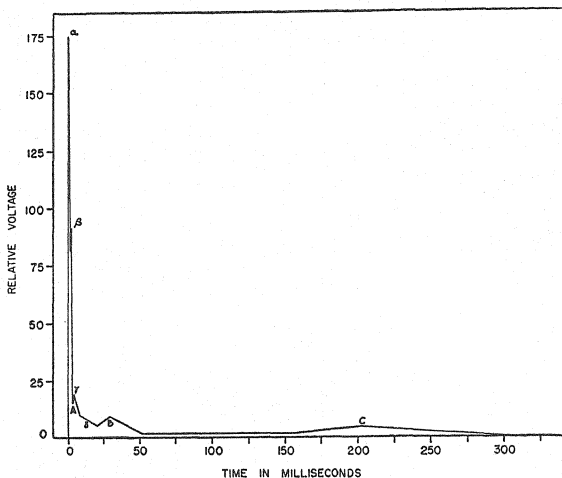


Figure 7-7. Magnitude and time of appearance of potentials following stimulation of a nerve containing fibers of several different diameters.

The first group of potentials (A, including alpha, beta, and gamma divisions) appears under the recording electrode within a few milliseconds. A second group of potentials, labeled B, arrives at around 25 to 35 milliseconds, and a third group, labeled C, appears under the recording electrode during the period from 160 to 250 milliseconds after the time of stimulation. (Reproduced by permission from Erlanger and Gasser, *Electrical Signs of Nervous Activity*. Copyright, 1937, by University of Pennsylvania Press.)

in mammals is at a rate of about 300 feet per second and in the slowest fibers the rate is only a few feet per second. In general, there is a relationship between the diameter of the fiber and the rate of conduction of impulses, the rate being faster, the larger the fiber. Also, the larger fibers have a lower threshold for electrical stimulation. When a nerve, which is composed of fibers of several diameters, is stimulated, and the passage of impulses is recorded at a point at some distance from the stimulating electrode, the impulses traveling in the large fibers are recorded as a first wave, and those in the medium size and smaller fibers produce second and third waves respectively. This is illustrated in Figure 7-7.

Use of Simple Electrical Stimulating Devices

Many of the experiments performed in the physiological laboratory involve the use of simple electrical stimulating devices and kymographic recording. The practical use of these will be described briefly.

Direct current. The simplest circuit that can be used for electrical stimulation of tissues, as shown in Figure 7-8, includes a battery, a key, and the tissue to be stimulated. On closing the key, the circuit is completed and the amount of current which flows depends upon the voltage of the battery and the total

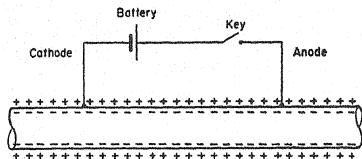


Figure 7-8. Simplest circuit for stimulation with direct current.

resistance in the circuit. Observe that two electrodes are applied to the fiber; the electrode which is connected with the negative pole of the battery is known as the *cathode* and the one connected to the positive pole is the *anode*. Current will continue to flow in the circuit until the key is opened, then the flow will cease. Closing and opening the circuit by means of the key is referred to as *making* and *breaking* the circuit.

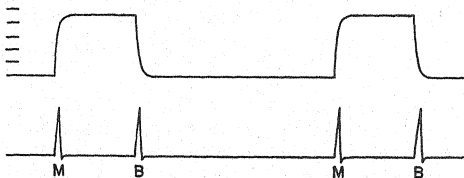


Figure 7-9. Stimulation with direct current.

Upper record shows level of current in the circuit and lower record shows responses of muscle. Current level is zero when key is open. When circuit is closed, indicated by M, the current mounts rapidly and the muscle momentarily contracts. Current continues to flow while the circuit remains closed, but no further response of the muscle is seen. At B the key is opened; current drops rapidly to zero and another response of the muscle is elicited.

If the current is of sufficient strength, the nerve is stimulated *at the time the circuit is closed and again when the circuit is opened*. No response is observed during the periods between manipulations of the key. This is illustrated in the diagram. In other words, a change in current from zero up to a certain level will excite, and a change from this level down to zero also will excite, but current flow at a constant level in this range does not stimulate the fiber.

Another fact concerning effects of direct, or *galvanic*, current on irritable tissues is that the stimulation occurs *at the cathodal electrode when the circuit is made and at the anodal electrode when the circuit is opened*.

It is true, also, that the "make" stimulus is more effective than the "break" stimulus when direct currents are used. This is related to changes at the electrodes and in the tissue occurring during the flow of the current.

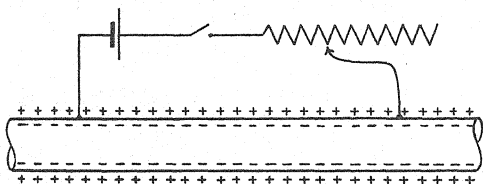


Figure 7-10. Circuit for stimulating with direct current.

Rheostat is included so that resistance, and hence strength of current, can be varied.

In the circuit diagrammed in Figure 7-8 there is no provision for changing either the voltage or the resistance and hence no method for altering the intensity of the current. In practice, when direct current is used, a variable resistance is obtained by including in the circuit a length of high-resistance wire or some other suitable device (rheostat). In Figure 7-10 as the connection of the electrode on the right with the high resistance is moved further to the right, a greater length of wire and hence more resistance is included in the circuit, and the intensity of the current is proportionately decreased. By the use of this type of preparation it can be shown that a current strength which is barely effective on the "make" will not elicit a response on the "break," and a current which is barely sufficient to produce a maximal response on the "make" will produce a submaximal response on the "break." When the current is still greater, a maximal response is produced by each "make" and "break" stimulus, as shown in Figure 7-9.

Induced current. For stimulation of tissues induced, or *faradic*, current commonly is used. Some of the reasons for this become apparent as one considers the mode of production and the characteristics of induced current. If current is made to flow in a wire or if the flow of current is altered in strength,

current is induced in a second wire placed close to the first. As current flows in a wire, the wire is surrounded by a whirl of magnetic lines of which the wire is the axis, and the inductance of current in an adjacent wire is due to the cutting of that wire by these lines of magnetic force. The *strength of the induced current* is determined by the *changes in current* in the first wire and by the *position* of the second wire with reference to the first. Current in the second wire varies directly with the *rate of change* of current in the first, and

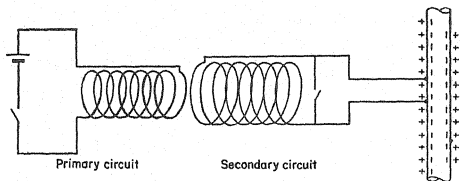
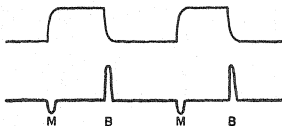


Figure 7-11. Essential features of the apparatus for stimulation with induced current.

A *primary circuit*, shown on the left, includes a battery, a key, and the primary coil. A *secondary circuit*, shown on the right, includes a secondary coil and the tissue which is to be stimulated. The secondary circuit also includes a short-circuiting key.

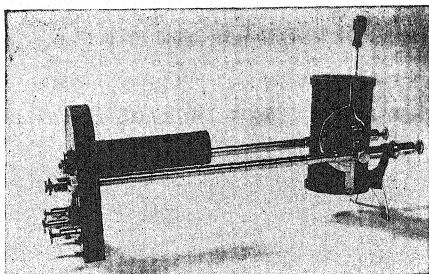
Figure 7-12. Diagram of current flow in primary circuit (*above*) and secondary circuit (*below*) during "make" and "break" of the primary circuit.



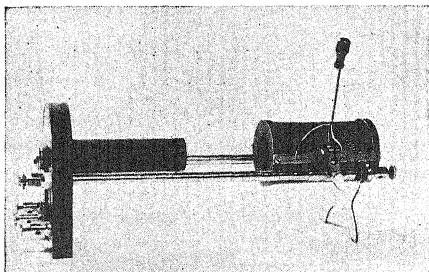
it is greater, the shorter the distance between the two wires. Finally, current in the second wire is greatest when the wires are parallel to each other and approaches zero as the second wire is rotated toward a position perpendicular to the first wire. These facts concerning induced currents are utilized in constructing the inductorium which is used as a stimulating device in the physiological laboratory.

The construction and use of the inductorium. The inductorium consists of two coils of wire: a primary coil of a relatively small number of turns of fairly stout wire, and a secondary coil of many more turns of much finer wire. The strength of current induced in the secondary coil can be increased by placing inside the primary coil a core consisting of a bundle of soft iron rods. The iron rods serve to increase the number of lines of magnetic induction which pass

The secondary coil is at a distance of 12 cm. from the primary coil, and the axis of the secondary coil is as near the perpendicular to the axis of the primary coil as it can be placed. This results in the lowest current that can be induced in the secondary with a given change in intensity of current in the primary circuit.



The secondary coil is at a distance of 12 cm. from the primary and its axis has been rotated to the horizontal position so as to be in line with the axis of the primary coil. Greater induced currents are obtained as the secondary coil is set closer to the horizontal position. A further increase in intensity of induced current is obtained by moving the horizontal secondary coil closer to the primary.



The secondary coil is shown moved to zero distance from the primary. At this setting the current induced in the secondary coil is the greatest that can be obtained during any given change of current in the primary circuit.

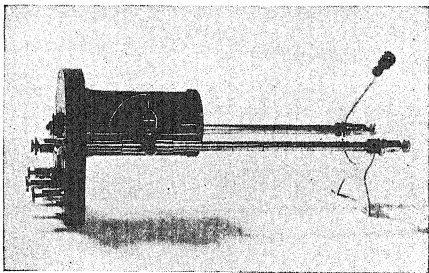


Figure 7-13. Inductorium.

through the core from end to end and return outside through the air. By the formation of these lines the core itself becomes magnetized, and when they disappear it becomes demagnetized. The secondary coil is wound on a large hollow spool which can be moved over the primary or withdrawn and turned at various angles with the axis of the primary. *Thus, the induced current may be caused to vary from zero when the secondary is withdrawn and turned at right angles to the primary, up to the maximum when the secondary covers the primary.* Hence it is possible to increase the current step by step from sub-threshold levels up through effective ranges to the supramaximal level.

As already noted, the current is induced in the secondary coil only when there is an alteration of the strength of current in the primary. When that change is sudden, as on making or breaking the primary circuit, the induced

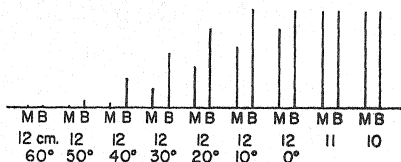


Figure 7-14. Response of muscle to induced current.

M = make, B = break. Cm indicates, in centimeters, the distance the secondary coil is moved horizontally away from the position where it surrounds the primary. The angle of the secondary coil with the horizontal is indicated in degrees. The standard procedure is to start with the secondary coil at 12 cm. and near the vertical position, then to obtain greater induced current in the secondary, first by rotating the secondary coil toward the horizontal. If still greater intensity is desired after the secondary coil has been placed in the horizontal position, then it is moved closer to the primary coil.

current develops suddenly and is of brief duration. The induced current produced by the making of the primary circuit runs opposite to the direction of the current in the primary; thus, if the current runs clockwise in the turns of the primary coil, the induced current runs counterclockwise in the turns of the secondary. On breaking the primary circuit, the induced current is in the same direction as was the current in the primary before the break, and in the opposite direction of the current induced in the secondary coil when the circuit was made.

Since the currents induced in the secondary coil occur during the change of intensity of the primary, there is a current in the secondary only during the formation of the primary current and again at the instant that the primary is broken. The induced current (as shown in Figure 7-12) is less intense at the make than at the break. Therefore, *when induced current is used the make shock is less effective than the break.* It should be noted that this is the reverse of what is observed when direct current is used.

It is frequently desirable to have a series of rapidly repeated stimulations. Instead of making and breaking the primary current by hand, it is possible to produce automatically a series of rapid stimulations by means of a mechanical interrupter on the inductorium. The current in the primary circuit may be made to pass through a screw, the point of which is in contact with a flat spring. The flat spring is connected with the primary coil. When the circuit is properly made, the current passes through the screw to the spring and thence through the primary coil, magnetizing the iron core. The magnetized core pulls the iron disk fastened to the spring and thus breaks the circuit between the spring and the screw. As the current is no longer flowing, the core becomes demagnetized, the iron disk is no longer pulled, and the spring flies back against the screw. The circuit is again made and the process again repeated. Thus, the primary circuit is rapidly made and broken, and with each make and break a current is induced in the secondary coil. The quickly alternating induced currents form the so-called "tetanizing" current.

Kymographic recording. Sometimes physiological processes are so rapid that it is impossible for the eye to follow them, and sometimes they are so slight that they must be magnified in order that they may be studied. Also, in many cases it is desirable to have permanent records of what has taken place. For these reasons devices have been invented for recording all manner of physiologic changes. The most generally applicable of the instruments for securing a continuous objective record are the kymograph and the writing lever. The kymograph consists of a cylindrical drum which is rotated about its axis at a fairly uniform rate by a mechanism with an adjustable speed. The drum of the kymograph presents a steadily moving surface on which physiological processes can be recorded. The surface is usually glazed paper, coated with a film of soot; the record is made by a writing point rubbing off, as it moves, a trace in the film of soot. After a record has been made, the paper is removed, passed through a solution of shellac, and dried. Thus, a permanent white-on-black record is obtained.

Chapter 8

EFFECTS OF IMPULSES AT THE NEUROMUSCULAR JUNCTION AND AT SYNAPSES

The Motor Unit

The motor nerve supply to skeletal muscle comes from large cell bodies located in the anterior columns of gray matter in the spinal cord and in specific nuclei in the brain. Each of the cell bodies in the spinal cord gives rise to an axon which leaves the cord by a ventral root and continues

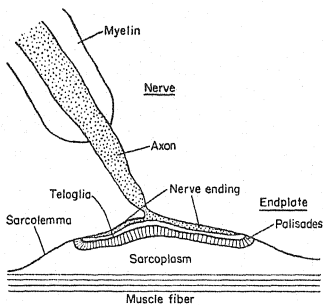


Figure 8-1. Diagram of structures at the motor end plate.

without interruption to the muscle which is innervated. The axon divides as it approaches the muscle, to give rise to a number of branches each of which innervates a single muscle fiber. A single motor neuron and the considerable number of muscle fibers which it innervates comprise a

motor unit. This is the smallest functional unit of the motor system. Under physiological conditions, skeletal muscle contracts only when it is activated through its motor nerve supply and the impulses are set up at the motor neuron cell body, or soma, in the central nervous system.

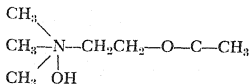
The connection between the nerve ending and the muscle fiber is the *neuromuscular junction* and the structures at the neuromuscular junction constitute the *motor end plate*. The principal anatomical features of the motor end plate are shown diagrammatically in Figure 8-1.

Transmission of Excitation at the Neuromuscular Junction

In mammals, under normal conditions, each impulse which travels along a terminal branch of the axon of a motor nerve causes depolarization at the motor end plate, and, after a brief delay, a muscle impulse is conducted in each direction from the end plate. In the wake of each muscle impulse, contraction develops. If the ends of the muscle fiber are free to move, the fiber shortens, or, if the ends of the fiber are fixed so that the muscle cannot shorten, an increased tension develops. The former type of contraction is known as *isotonic* (change in length with constant load), and the latter as *isometric* (change in tension with constant length). While the muscle fiber still is contracted, further contraction occurs if the motor nerve is stimulated again. Thus, a step-like contraction, known as *wave summation*, can be produced by a series of closely spaced stimuli. This is illustrated in Figure 8-2. As previously explained in the discussion of refractory periods, if the nerve is stimulated again too soon after the first stimulus, the nerve fiber will not respond to the second stimulus.

The liberation and action of *acetylcholine* at the motor end plate is an indispensable part of the process of transmission of excitation at the neuromuscular junction. The essential steps are as listed below:

Nerve impulse arrives at neuromuscular junction → Liberation of acetylcholine → Local depolarization of end plate by action of acetylcholine → Depolarization of muscle fiber by end plate potential → Propagated muscle impulse → Propagated wave of contraction.



Formula
of acetylcholine

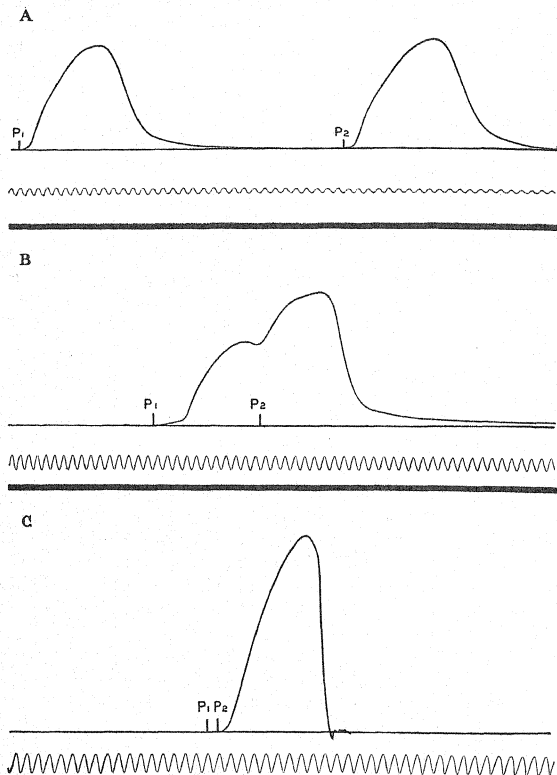
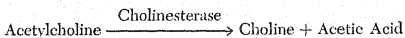


Figure 8-2. Wave summation.

Effects of two successive stimuli of identical strength, P_1 and P_2 , applied closer and closer together. Tuning fork record shows time in hundredths of a second. (Reproduced by permission from Halliburton and MacDowall, *Handbook of Physiology*. Copyright, 1930, by The Blakiston Co.)

The view that acetylcholine (abbreviated Ach) is concerned with neuromuscular transmission is based largely on the following observations. First, stimulation of a motor nerve causes liberation of Ach. This is demonstrated by perfusing Locke's solution through the blood vessels of a muscle and testing the perfusate for its Ach content before and after stimulating the motor nerve. To the Locke's solution used in such experiments there must be added a small amount of eserine, a substance that prevents the action of the enzyme which destroys Ach. Second, *cholinesterase*, the enzyme which promotes the hydrolysis of acetylcholine into choline and acetic acid, is present in large concentrations at the motor end plate.



Third, the injection of acetylcholine into the arterial blood supply of the muscle causes a brief muscular contraction similar to that produced by stimulating the motor nerve to the muscle. Thus, it is seen (1) that motor nerve stimulation causes liberation of Ach, (2) that Ach is capable of initiating muscular contraction, and (3) that an enzyme which will quickly inactivate the Ach is concentrated at the neuromuscular junction.

There are two corollaries to the theory that transmission of excitation at the neuromuscular junction is accomplished through the action of Ach. First, anything which makes the neuromuscular junction refractory to the action of acetylcholine should prevent the muscle from responding to nerve stimulation. This has been found to be true for certain drugs. *Curare* decreases the excitatory effect of acetylcholine in proportion to dosage, and, at the same time, it decreases or blocks the response to nerve stimulation. Furthermore, curare produces paralysis even though there is no defect in the conduction of the nerve impulse and even though the muscle itself will contract in response to direct electrical stimulation. This establishes the fact that the neuromuscular junction is the site of the block interposed by curare.

A second corollary to the chemical theory is that anything which promotes the accumulation of acetylcholine at the neuromuscular junction, for example, prevention of the action of the cholinesterase, should have acetylcholine-like influences on neuromuscular transmission. Several such *anticholinesterases* are available.¹ When these substances are applied to the neuromuscular junction in proper amounts, they produce hyper-

¹ Neostigmine, eserine, and di-isopropylfluorophosphate.

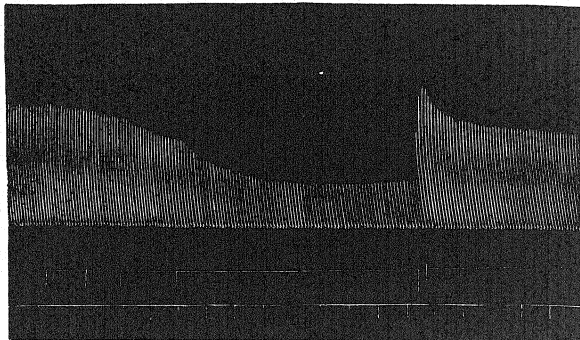


Figure 8-3. Effect of curare on neuromuscular transmission, and anti-curare effect of potassium.

Twitches of the *tibialis anticus* muscle of the dog in response to supramaximal stimuli applied to its motor nerve at a rate of once per second are recorded. The bottom line shows time in 10-second intervals. The straight line above the time line indicates procedures. A curare preparation was given intravenously at the times indicated by the first four downstrokes. Thus, curarization of a degree sufficient to cause about half of the muscle fibers to fail to respond was attained. At the time of the next downstroke on the procedure record a small amount of potassium chloride was injected into the artery which carries blood to the *tibialis anticus* muscle.

excitability to the extent that a single nerve impulse may cause repetitive muscle impulses and, consequently, a more prolonged contraction.

The abnormal states of irritability at the neuromuscular junction which are produced, as described above, by drugs in the normal animal have their counterparts in disease. For example, in *myasthenia gravis* (severe muscular weakness) the defect closely resembles incomplete curarization. The patient is much more sensitive than normal subjects to the action of curare and the *anticholinesterases* are of great benefit in the relief of the muscular weakness.

Contraction of Skeletal Muscle

A sustained contraction of a muscle is accomplished through rotational activation of muscle fibers so that the total number of active fibers in the

muscle at a given time remains relatively constant. It is common practice to refer to quick changes in length or tension of a muscle as contraction, while the sustained tension is known as *tonus*, although fundamentally, in mammals, contraction and tonus are different only quantitatively.

For experimental purposes a muscle may be made to contract by direct electrical stimulation of its motor nerve. It is a simple laboratory procedure to isolate the gastrocnemius muscle of a frog, keeping the motor

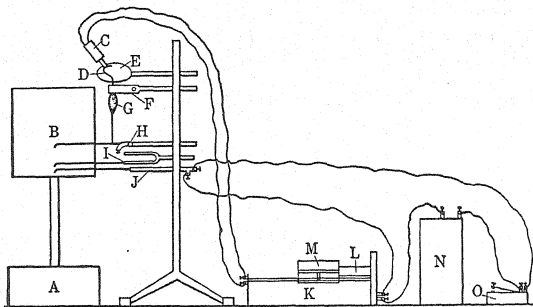


Figure 8-4. Setup for recording contraction of isolated gastrocnemius muscle of the frog.

Induced current is used. A, kymograph; B, smoked drum; C, stimulating electrode; D, nerve; E, nerve holder; F, muscle clamp; G, muscle; H, muscle lever; I, tuning fork for time record; J, signal magnet to indicate time of stimulation; K, inductorium; L, primary coil; M, secondary coil; N, dry cell; O, key. If time relationships are not being studied the tuning fork and signal magnet records can be omitted. (Reproduced by permission from Cook, *Elementary Human Physiology*. Copyright, 1936, by Harper and Brothers.)

nerve to the muscle intact, and to activate the muscle either by stimulation of the nerve or by applying the stimulating electrode to the muscle. A diagram of the preparation is shown in Figure 8-4.

When a single supramaximal stimulus is applied to the motor nerve, impulses are set up simultaneously in all of the nerve fibers and, within a fraction of a second, a sudden "twitch" of the muscle is produced. The amplitude of the twitch depends upon several factors including the weight being lifted, the temperature, and previous activity. In the case of the muscle twitch, contraction is set up in all of the muscle fibers more

synchronously than ever occurs under physiological conditions. In the intact animal, impulses are set up in the motor neuron somas in the central nervous system. Impulses impinge upon these from many sources. Some of the impulses reaching the motor neuron soma have an excitatory effect, others are inhibitory, and the response of the neuron is the resultant of these influences. There is no physiological mechanism by means of which all of the motor neurons supplying a given muscle are activated simultaneously and only a single time, as may be the case when the motor nerve is stimulated artificially. Under physiological conditions the activation of motor neurons supplying a given muscle is asynchronous and repetitive.

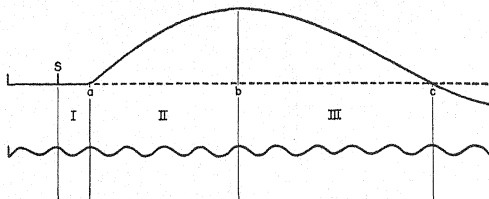


Figure 8-5. Phases of a single muscle twitch produced by direct stimulation of its motor nerve.

S indicates time of stimulation. Phase I is the latent period, phase II is the period of contraction, and phase III is the period of relaxation. The lower record shows time in hundredths of a second.

When the motor nerve is stimulated repeatedly at a fast rate, the muscular twitches become fused, with the result that a smooth sustained contraction is produced. This is called *tetanus*. At somewhat slower rates, the muscle does not have time to relax completely, and a jerk is seen to be associated with each *colley* of nerve impulses. This type of response is known as incomplete tetanus (Figure 8-6).

Source of energy for muscular contraction. When a muscle contracts, it may perform mechanical work which is expressed in terms of weight lifted through a vertical distance. Also, a considerable amount of heat is evolved from contracting muscles. Ultimately, skeletal muscle obtains energy for its activity by the oxidation of organic compounds. The potential energy in such compounds is released during oxidation and is made available for use by the contracting muscle. A complex series of reactions

occurs by means of which glycogen and oxygen are fed into the muscular machine, and carbon dioxide and water are produced as waste products.

The oxygen consumption and carbon dioxide production of the body increase with increasing muscular activity. In severe exercise, the uptake

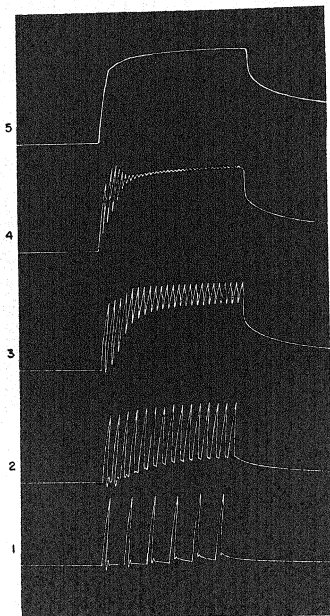


Figure 8-6. Stimulation of isolated muscle at several different rates.

Rates progressively increase from below upwards. (Reproduced by permission from Howell, *Textbook of Physiology*. Copyright, 1940, by W. B. Saunders Co.)

of oxygen may increase to ten times the level found at bed rest. The ventilation of the lungs is greatly increased by an increase in rate and depth of breathing and the output of the heart is increased several fold. Also, more oxygen is given up to the active tissues per unit volume of

blood flowing through the tissue. However, in severe muscular exercise, even though the oxygen uptake is greatly increased it still does not keep pace with the body's need for oxygen. The accumulation of organic acid metabolites occurs regularly in severe muscular exercise so that after the exercise ceases a considerable amount of oxygen still is needed to oxidize the excess acid. Therefore, oxygen consumption will continue at a level higher than the basal rate of consumption for a while after cessation of exercise, but will decrease steadily toward the basal level. Thus, the *oxygen debt* which was incurred during exercise is progressively repaid during the next five to fifteen minutes after cessation of the exercise.

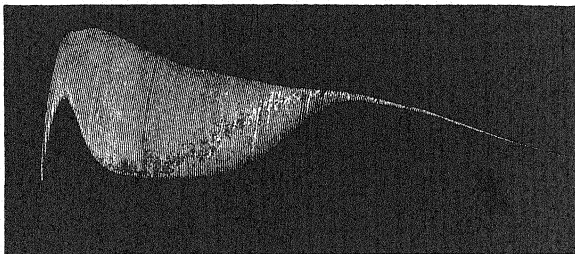


Figure 8-7. Fatigue curve from isolated skeletal muscle.

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Fatigue. Fatigue is a state of decreased activity due to previous activity. When the isolated gastrocnemius muscle of the frog is stimulated through its motor nerve supply at a rate of once or twice per second, characteristic changes in the ability of the muscle to contract and to relax are observed. The typical "fatigue curve" obtained under these conditions is illustrated in Figure 8-7. At first, the amplitude of the contraction may increase a little and then a gradual diminution in amplitude is seen. Impaired relaxation, or *contracture*, is evident also as stimulation is continued. The rapid fatiguing of isolated skeletal muscle is related largely to the lack of a blood supply, since wastes are not removed and the supply of oxygen and glucose is not maintained. When the motor nerve to a muscle with intact blood supply is stimulated for a prolonged period, the amplitude of the contraction eventually will show a decrease, and, when

this has occurred, the injection of epinephrine into the artery supplying the muscle will temporarily restore the amplitude of contractions.

Failure of skeletal muscle to contract in response to stimulation of the motor nerve, theoretically, could be related either to failure of the nerve to conduct impulses or to failure of neuromuscular transmission or to failure of the contractile process. Actually, the latter is concerned, and it is probable that the supply of one of the chemicals needed for contraction decreases sufficiently to become a limiting factor.

Independent irritability of muscle. Muscle fibers may be activated by direct electrical stimulation instead of by the motor nerves. However, since the motor nerve fibers have a lower threshold than the muscle fibers, special methods must be used to demonstrate the independent irritability of muscle. The classic experiment was done by Claude Bernard, a famous French physiologist of the previous century. He demonstrated that after curarization, the nerves were still stimuable and capable of conducting impulses, but the muscle failed to respond to nerve stimulation. However, the muscle of the curarized preparation would respond to direct electrical stimulation.

In some muscles the distribution of the nerve endings is so diffuse that, if the nerves are viable, the muscle is stimulated indirectly by activation of the nerve endings, even though the electrodes are applied directly to the muscle. This is true of the gastrocnemius in which the muscle fibers are arranged as in a feather, and nerve endings are distributed throughout the length of the muscle. In the sartorius muscle of the frog, on the other hand, there are long parallel muscle fibers and the nerve fibers are confined to one end; therefore, at the other end it is possible to stimulate the muscle fibers directly. Also, in man, when a motor nerve has been cut and degenerates so that it is no longer stimuable, one can stimulate the muscle fibers directly, if direct current is used. Induced current which is of brief duration is ineffective.

Transmission at Synapses

Anatomical features. A synapse is the site of contact, or the junction, between the cell walls of two neurons at which excitation or inhibition normally is transmitted. Commonly, the termination of a branch of the axon of one neuron expands into a bulbous ending that comes in contact with a dendrite or cell body of another neuron. This type of ending is

known as a terminal foot or knob. See Figure 8-8. Some of the neuron somas—for example, the motor neurons in the anterior gray columns—are contacted by large numbers of terminal feet supplied by a considerable number of neurons. The innervation of a single neuron by a number of neurons is known as *convergence*. Conversely, a single neuron may have synaptic connections with a number of neurons, and this is called *divergence*. Thus, there is, through synaptic connections, a basis for influences from various sources to converge upon a given neuron and for impulses over a single pathway to diverge and activate several pathways.

Effects of impulses at synapses. Ordinarily, a neuron is activated under physiological conditions only when impulses reach it almost synchronously at a number of adjacent terminal feet. In other words, a single impulse arriving at a single terminal foot fails to cause the neuron to conduct an impulse; additive excitatory effects of a number of impulses are necessary before the neuron is “fired.” The single impulse arriving at the single synapse may be visualized as constituting a subliminal stimulus, and the *summation* of such stimuli is necessary to result in activation of the neuron. As previously described, this type of process can be illustrated by the use of barely subthreshold electrical stimuli applied to nerve fibers. The nerve fiber does not conduct an impulse after one such stimulus, but will conduct in response to a second or third if the stimuli are closely spaced. It is evident that a subthreshold stimulus lowers the threshold for a brief period and that the effects of a series are additive, that is, they summate, so that finally one of the subthreshold stimuli may produce a response of the same type as that which can be elicited by a single effective stimulus. Summation is of two main types. The summation of the local excitatory effects of impulses arriving at adjacent terminal feet is known as *spatial* summation, while any summation related to successive impulses at a single terminal foot is called *temporal* summation.

For temporal summation to occur at a terminal foot the excitatory state produced by the first impulse must persist for a time at least as long as the absolutely refractory period of the nerve fiber, otherwise a second impulse could not be set up to arrive at the synapse soon enough for its influences to be added to the effects of the first. It appears that temporal summation is of negligible importance at some synapses, especially in the central nervous system, but there is evidence that it may be of considerable importance at the synapses in autonomic ganglia.



Figure 8-8. Cell body of a neuron in the spinal cord showing terminal feet in contact with the cell surface.

About 100 terminal feet were counted contacting this cell; however, less than half of these can be seen at this one focus. (By permission after Creed, Denny-Brown, Eccles, Lidell and Sherrington, *Reflex Activity of the Spinal Cord*. Copyright, 1932, by Oxford University Press, from original figure by E. C. Hoff.)

Chemical influences at synapses. Another observation that has a bearing on the problem of synaptic transmission is that following repeated strong stimulation of the preganglionic fibers which innervate the nerve cells in autonomic ganglia (see next chapter) the ganglion cells may continue to discharge impulses for a brief period after impulses are no longer reaching them. One must conclude that the excitatory influence of the preganglionic impulses persists for a number of milliseconds at a level such that the ganglion cells may discharge, then recover and respond again several times before the environment of the cell returns to the previous non-stimulatory state. This is illustrated in Figure 8-9. Such a

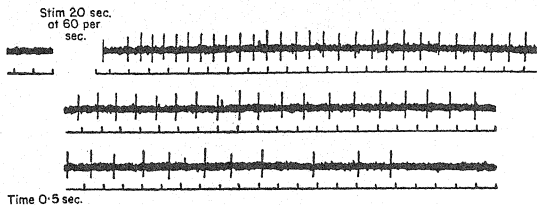


Figure 8-9. After-discharge of cells in a sympathetic ganglion.

Preganglionic fibers were stimulated at a rate of 60 per second for 20 seconds at the period indicated. The record shows action potentials recorded from the postganglionic fibers. The three portions of the record are consecutive. It is seen that impulses appear with decreasing frequency for a period of 27 seconds after cessation of preganglionic stimulation. (By permission from Bronk, *J. Neurophysiol.*, Vol. 2, p. 387, 1939.)

result is readily explained if one postulates that the nerve impulses cause liberation of an excitatory substance when they arrive at the synapses. In fact, it is known that both acetylcholine and potassium ions are liberated in autonomic ganglia when the presynaptic fibers are stimulated, and it has been demonstrated by studies involving perfusion of the ganglia that these substances have an excitatory action on the ganglion cells (Figure 8-10). Also, perfusion of the ganglion with an anticholinesterase increases the response of the ganglion cells to preganglionic stimulation.

Transmission at some of the synapses in the central nervous system involves processes which thus far have not been encountered in autonomic ganglia. Notably, the motor neurons are brought under *inhibition* by the arrival of impulses at central synapses. How this occurs is not clear.

According to one hypothesis an inhibitory chemical is liberated at some synapses and an excitatory chemical at others. The nature of the inhibitory chemical mediator which has been postulated as yet has not been determined. Acetylcholine is produced in considerable amounts in some parts of the central nervous system, but in other parts little or no acetylcholine is found. At present it appears that acetylcholine plays a role in

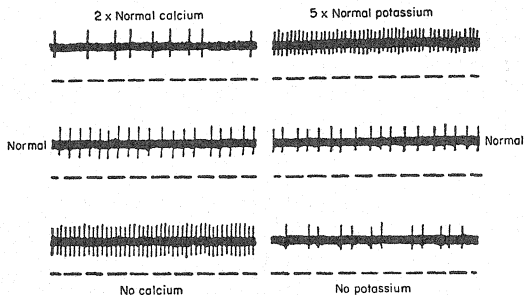


Figure 8-10. Stimulation of cells of sympathetic ganglion by acetylcholine and effect of calcium and potassium on the response.

The upstrokes in these records are action potentials recorded from single postganglionic fibers; hence, they indicate the rate of discharge of a single ganglion cell. When the two middle records, labeled "normal," were obtained the ganglion was being perfused with a solution containing 40 micrograms of acetylcholine per ml. and containing calcium and potassium in the concentrations found in Ringer's solution. The other records show effects of increasing and decreasing the calcium and potassium concentrations while keeping the solution otherwise unchanged. It is demonstrated that a decrease in the Ca/K ratio results in an increased rate of discharge in response to a given acetylcholine concentration. (By permission from Bronk, *J. Neurophysiol.*, Vol. 2, p. 293, 1939.)

synaptic transmission in autonomic ganglia and perhaps mediates excitation at some synapses in the central nervous system, but probably it is not an important factor at other central synapses.

Synaptic resistance. The fact that a single impulse may have an influence like a *subliminal* stimulus at the synapse is an essential feature of the functioning of the nervous system. Unlike the situation at the skeletal neuromuscular junction, there is resistance to the passage of an impulse at the synapse and this must be overcome by summation if the next

neuron is to be "fired." Hence the paths over which impulses will pass, once they enter the central nervous system by the efferent nerves, are determined not only by the richness of the synaptic connections in the pathway but also by the number of impulses which enter by the afferent nerves during a given period. If the synapses offered no resistance, that is, if there were a 1:1 ratio of presynaptic impulses to postsynaptic impulses, a single impulse entering the central nervous system would spread to as many neurons as can be activated by a large number of impulses. It is apparent that synaptic resistance is essential in the adjustment of the degree of response in the nervous system to gradation of intensity of stimulation. The effect of decreasing the resistance at the synapse is illustrated in an animal under the influence of a large dose of strychnine. In this case the slightest activation of afferent pathways is followed by a convulsion which is the consequence of widespread, indiscriminate activation of motor neurons.

A number of compounds have been studied which are capable of lowering the excitability at synapses in autonomic ganglia, so that either more presynaptic impulses are required to set up postsynaptic impulses or the ganglion cells become completely unresponsive to presynaptic impulses. Nicotine, applied directly to the ganglia, commonly was used to block synaptic transmission in the earlier studies, and at present the most useful compound for this purpose is tetraethyl ammonium bromide or chloride. It is noteworthy that such substances also decrease the responsiveness of the ganglion cells to acetylcholine.

Chapter 9

NEURAL CONTROL OF SMOOTH MUSCLE AND SECRETORY CELLS

Visceral Effectors

The term *effector* refers to the cells and tissues which are innervated by efferent nerves. These cells characteristically are capable of responding to impulses reaching them by their efferent nerve supply. The effectors, other than skeletal muscle, include smooth muscle, the specialized conducting system of the heart, heart muscle, and the secretory cells of glands. The latter effectors are known collectively as *visceral* effectors, and the efferent nerves which innervate them constitute the *autonomic nervous system*.

Secretory cells are found in the exocrine and endocrine glands. Notable examples of exocrine glands are the salivary glands, the pancreas, the minute glands of the mucosa of the digestive tract and respiratory tract, sweat glands, tear glands, etc. The adrenal medulla is an example of an endocrine gland, the secretory activity of which is mainly or exclusively controlled through its efferent innervation.

Smooth muscle is found in the walls of most of the tubular and globular organs of the body: stomach, intestine, respiratory passages, urinary bladder, gall bladder, blood vessels, etc. Also, it is found in the skin in the form of the piloerector muscles which, on contraction, cause the hairs to assume a position more nearly perpendicular to the skin. In the eye, the radial and circular muscles of the iris which serve to determine the size of the pupil are composed of smooth muscle.

The role of smooth muscle in specific organs will be considered in subsequent sections dealing with organs and organ systems. At this point, some facts which are applicable to smooth muscle in general and,

especially, the mechanism of transmission of influences from the efferent nerves to smooth muscle will be presented.

The Autonomic Nervous System

Unlike skeletal muscle, most smooth muscle is supplied with *two* types of efferent nerves, one set of nerves being *inhibitory* and the other set *excitatory*. The entire distance from the neurons in the central

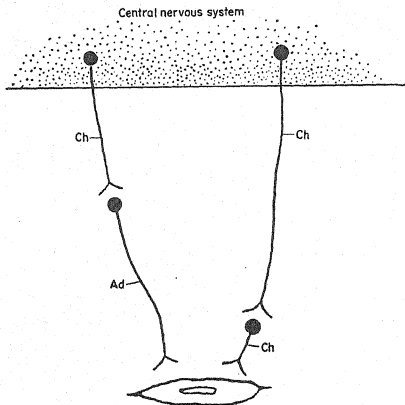


Figure 9-1. Diagram of innervation of typical visceral effector cell.

A smooth muscle cell is shown to be innervated by two sets of efferent pathways. The sympathetic pathway is shown on the left and the parasympathetic pathway is illustrated on the right. A synapse is interposed in each pathway. The preganglionic fibers in both pathways are cholinergic (Ch) the postganglionic fiber in the parasympathetic pathway usually is cholinergic also, while the postganglionic fiber in the sympathetic pathway shown is adrenergic (Ad).

nervous system to the effector is traversed by a single axon in the case of skeletal muscle, whereas a synapse is interposed and a second neuron is present in the pathway to the visceral effectors. In the latter case an axon, or *preganglionic* fiber, travels out from the cell body in the central

nervous system and makes synaptic connections with the cell body of a second neuron. The cell bodies of the second neuron of the pathway are found in *ganglia* which may be distinguished as enlargements on the nerve or which lie within the organ innervated. The axons which pass from the ganglia to the effector cells are known as *postganglionic* fibers. Typically, a visceral effector cell receives one set of fibers from either cranial or sacral nerves and the other set comes from the thoracic or lumbar part of the spinal cord. Therefore, the autonomic system is divided into a *cranio-sacral*, or *parasympathetic* portion, and a *thoraco-lumbar* or *sympathetic* portion. The general distribution of these systems is illustrated in Figure 9-2.

The postganglionic fibers exert their actions on visceral effector cells through the liberation of chemicals. On the basis of the type of chemical mediator, they are divided into two groups, *cholinergic* fibers which liberate *acetylcholine* and *adrenergic* fibers which liberate *epinephrine* or *nor-epinephrine*. Smooth muscle of the intestinal wall, for example, is innervated by adrenergic fibers which have an inhibitory influence upon its motility and by cholinergic fibers which have an excitatory influence. Most of the adrenergic fibers innervating intestinal smooth muscle are sympathetic fibers, and most of the cholinergic fibers reaching it are parasympathetic fibers. When applied directly to the smooth muscle of the intestinal wall epinephrine produces inhibition; acetylcholine has an excitatory effect. Also, epinephrine or nor-epinephrine may be liberated into the blood from the adrenal gland and be carried to the intestinal smooth muscle where it produces inhibition.

Smooth muscle cells in other structures, as in the walls of the smaller blood vessels of the skin, show responses to epinephrine and acetylcholine which are the reverse of the responses of intestinal smooth muscle; they are contracted by epinephrine and nor-epinephrine or by their adrenergic nerve supply and are relaxed by acetylcholine. Whether a smooth muscle cell contracts or relaxes in response to epinephrine is determined by something within the cell, which is known either as the *receptive mechanism* or the *effector substance*. The two types of receptive mechanisms upon which epinephrine acts have been designated E and I, depending upon whether excitation or inhibition respectively, is produced. As a general rule, in dually innervated visceral effector cells the action of acetylcholine is opposite to that of epinephrine. Thus, increased motility of intestinal smooth muscle can be produced either by a decrease in epinephrine concentration or by an increase in acetylcholine concentra-

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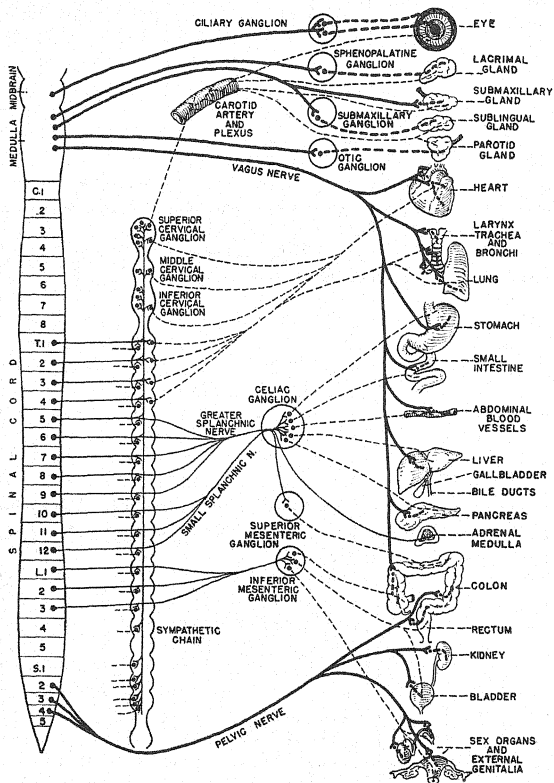


Figure 9-2. Diagram of distribution of the autonomic nervous system.

Heavy lines, the parasympathetic division; fine lines, the sympathetic division; continuous lines, preganglionic fibers; broken lines, postganglionic fibers. (From Youmans' Basic Medical Physiology.)

tion. As would be expected, compounds which block the action of cholinesterases have a stimulant action on intestinal motility and compounds which prevent the action of acetylcholine have an inhibitory action.

The pattern of innervation of secretory cells of glands is similar to that for visceral effector cells in general. Some secretory cells receive a dual innervation, but others are innervated by only a single set of nerves. As a general rule, the excitatory innervation of secretory cells is derived from

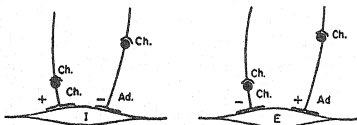


Figure 9-3. Diagram of innervation of two major types of smooth muscle classified on the basis of effects of epinephrine and acetylcholine.

In each of the two diagrams the parasympathetic innervation is shown on the left and the sympathetic innervation on the right. The type of smooth muscle on the left is inhibited by epinephrine and contracted by acetylcholine; the type on the right is contracted by epinephrine and inhibited by acetylcholine. E and I designate two types of "receptive mechanisms" in the cells which must be postulated to explain the fact that a single chemical, e.g., epinephrine, causes one cell to relax and the other to contract. (From Youmans, "Neural Regulation of Intestinal Motility." Copyright 1952 by *Amer. Jour. Med.*, Vol. 13, p. 213.)

the parasympathetic system and is cholinergic. For example, the stimulation of the *chorda tympani* nerve (parasympathetic) produces a copious flow of saliva. A similar effect can be produced by acetylcholine reaching the salivary gland by the blood stream, and the effects both of nerve stimulation and of injected acetylcholine can be prevented by certain drugs. The mechanisms for control of secretion by each of the more important glands is considered in subsequent sections.

Chemical Transmission in the Autonomic System

The evidence that visceral efferent nerves influence effector cells by the liberation of chemical mediators, namely, acetylcholine and epinephrine or nor-epinephrine, is of the same type as that presented in the discussion of transmission of excitation to skeletal muscle: (1) entrance of the substances into circulation from the effector when the efferent nerves are

stimulated, (2) actions of the substances on the effectors identical to those produced by nerve stimulation, (3) blockade of action of the substances and of the effects of nerve stimulation by the same drugs, (4) concentration in the effectors of enzymes capable of inactivating the chemical mediators, etc.

Cannon and co-workers introduced the term *sympathin* for the substance which enters circulation from visceral effectors as a result of stimulation of their adrenergic nerve supply. He postulated that sympathin is different from the chemical mediator itself which is liberated by the nerve ending. However, at present the substances produced at the nerve endings and entering circulation are considered to be epinephrine and nor-epinephrine in various proportions. The formulas for the chemical mediators are shown on page 404. Nor-epinephrine differs from epinephrine only in that the $-\text{CH}_3$ (methyl) group on the nitrogen atom is replaced by hydrogen.

Acetylcholine	Epinephrine	Nor-epinephrine
Cholinergic Mediator	Adrenergic Mediators	

Under physiological conditions the activity of visceral effector cells is influenced by reflexes just as skeletal muscle is under reflex control; however, the visceral organs are not under direct voluntary control as is the case for much of the skeletal musculature. Much of the regulation of the activity of visceral organs is accomplished through reflexes, and further regulation of these organs is achieved by means of hormones. A considerable part of some of the subsequent sections dealing with the physiology of the organs and organ systems will consist of descriptions of neural and hormonal control of specific visceral effectors.

Chapter 10

RECEPTORS. REFLEX ACTION

Receptors

Receptors are more or less specialized structures which are designed to set up impulses in afferent nerves in response to changes in environment. Many of the adjustments of the human body to changes in the external and internal environment which occur through neural mechanisms are elicited from receptors. The specialization of the receptor is such as to make it particularly responsive to a certain type of stimulus. In other words, although the receptor can respond to various types of stimuli, the energy change which is required to stimulate must be comparatively great, unless the stimulus is of the type to which the receptor is designed to respond. For example, the rods and cones in the retina of the eye are receptors which are specialized to respond to very small energy changes in the form of light, but they also will respond to a considerable energy change in the form of pressure, electric current, etc.

In the receptor, a local change becomes converted into nerve impulses which are propagated over the afferent nerve into the central nervous system, where they elicit responses that are determined by the anatomical connections. The only way by which a receptor can influence the afferent nerve ending supplying it, is to set up an all-or-nothing impulse. The message from the receptor to the central nervous system must, therefore, consist of one or more discrete, identical impulses. Variation in the message is accomplished only through variation in frequency of passage of the impulses. As explained in Chapter 8, gradation of response in the central nervous system to variation in frequency of arrival of impulses is accomplished through summation at the synapses.

Classification of receptors. Receptors have been classified on several bases. They may be subdivided into two major groups, *somatic* and *visceral*. The former includes the receptors in the skin and in skeletal

muscle, and the latter includes the receptors located in organs innervated by the autonomic nervous system. On the basis of point of origin of the stimulus, the receptors are divided into *exteroceptors* which respond to stimuli applied to the surface of the body or which come from a distance, *interoceptors* which transmit impulses from the viscera, and *proprioceptors* which are activated by changes in length or tension in skeletal muscle.

The terms *general* and *special* refer to extent of distribution of the receptors which are concerned, rather than to the degree of specialization histologically. The end organs for each of the special senses, which include sight, hearing, taste, and olfaction, are restricted to a small area. On the other hand, sensibility to touch, cold, warmth, and pain is present over the entire surface of the body.

On the basis of the nature of the stimulus to which the receptor is designed to respond, there are *photoreceptors* (light), *phonoreceptors* (sound), *chemoreceptors* (chemical agents), *pressoreceptors* (pressure), etc.

The purpose at this stage is to present certain functional characteristics which are common to all receptors, and the special features of responses of individual types of receptor will be considered in other connections.

Relation of stimulus to response. The response of a receptor to a sudden single change in its environment ordinarily is repetitive; a series of impulses is set up in the corresponding afferent nerve. This may be exemplified by the response of a muscle spindle in skeletal muscle. These receptors are sensitive to stretch, or passive lengthening, of the muscle. When there is no pull against the muscle, few or no impulses pass up the afferent nerve from the muscle spindle. When the muscle is suddenly elongated by applying a weight, there is a "burst" of impulses in the afferent nerve, occurring at a relatively high frequency, but becoming less and less frequent even though the new length is maintained. If the muscle is lengthened still more, there is another burst of impulses; and, as before, there is a steadily decreasing frequency even though the stretch is maintained.

The progressive decrease in frequency of impulse formation in the receptor, as conditions remain unchanged, is known as *adaptation*. The process differs from fatigue since the receptor is as capable as ever of responding to another change in the environment. The rate of adaptation in all receptors is related to the strength of the stimulus, but there are

wide variations in the rate of adaptation in different receptors; some types of receptor adapt very rapidly, while other types adapt slowly. The most rapid adaptation possible is that seen when only a single impulse is set up.

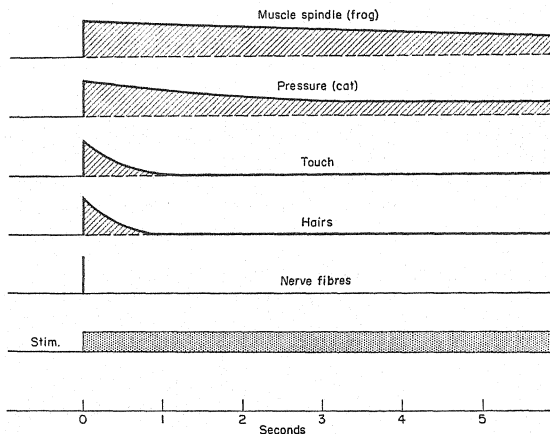


Figure 10-1. Diagram of rate of adaptation of receptors.

The height of the curve in each case indicates the frequency of discharge at the various times following the application of the stimulus. (After Adrian, *Basis of Sensation*. Copyright, 1928, by W. W. Norton & Co.)

Reflex Action

Reflex action is a type of activity which results immediately in response to impulses in afferent neurons. It is characterized by the predictable, stereotyped nature of the response. In general, when an afferent pathway is activated, either by electrical stimulation in the experimental animal or under physiological conditions, a reflex response results; and also a specific sensation, of a type depending on the nature of the receptors being stimulated, is elicited. The reflex response, however, occurs before one becomes

conscious of the stimulus which elicited it. In other words, reflex action is not only stereotyped, but also it is involuntary.

Reflex action may be elicited from virtually all of the receptors and, on the efferent side, either visceral effectors or skeletal muscle or both may be involved. On the basis of location of afferent and efferent pathways, reflexes may be classified in four major groups: (1) *somatic*, in which both afferent and efferent pathways are somatic (receptors are cutaneous or from skeletal muscle and skeletal muscle is the effector); (2) *visceral*, in which both afferent and efferent pathways are visceral; (3) *viscero-somatic*, in which the afferent pathway is visceral and the efferent pathway is somatic; and (4) *somato-visceral*, in which the afferent pathway is somatic and the efferent pathway is visceral. Examples of the latter three types of reflexes will be encountered in the subsequent sections dealing with organ systems. At this stage, the somatic reflexes will be described to establish an understanding of the essential features of reflex action.

Stretch reflexes and flexor reflexes. The reflexes which involve skeletal muscle are of two main types: stretch reflexes and flexor reflexes. The stretch reflexes also are known as tendon reflexes or as deep reflexes because they are elicited from receptors located in muscles and tendons. The flexor reflexes also are known as superficial or skin reflexes.

The *stretch* reflexes which have great importance under physiological conditions are, for the most part, *extensor* reflexes. The stretch reflex is exemplified best by the knee-jerk which occurs in response to tapping the patellar tendon. The sudden stretching of the quadriceps muscle stimulates receptors in the muscle or tendons, so that a reflex shortening occurs. The physiological role of the stretch reflexes is to cause sustained tonus in muscles which are concerned with the maintenance of posture (page 129). For example, when a person is standing, the tension on the extensor muscles in the legs causes these muscles to be under constant reflex excitation from the receptors located in the muscles. Consequently, a sufficient tonus level is maintained in the extensor muscles to prevent the legs from bending under the weight of the body. The stretch reflex is comparatively simple in that the afferent nerves which are concerned connect directly with motor neurons some of which are in the same segment of the spinal cord on the same side and the efferent nerves for the response connect with one or a few muscles.

The *flexor* reflexes are protective in function. They constitute a quick involuntary mechanism for withdrawal of a part of the body from a pain-

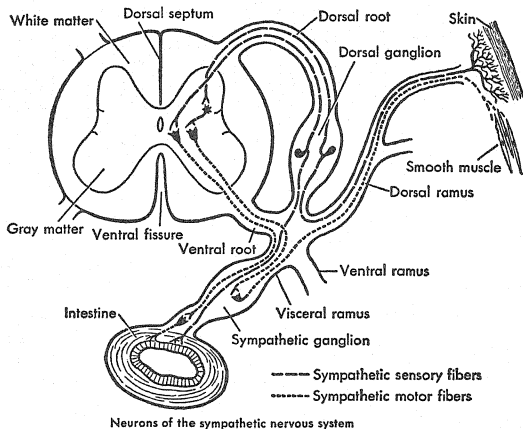
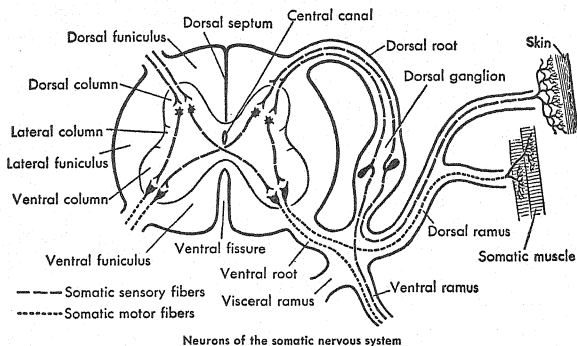


Figure 10-2. Diagrammatic transverse sections of the spinal cord.

In the upper drawing, reflex connections from the skin to skeletal muscle are shown. In the lower drawing, details of the sympathetic pathway are shown. (Reproduced by permission from Mavor, *General Biology*. Copyright, 1947, by The Macmillan Company.)

ful or damaging type of stimulus. Application of such a *noxious* stimulus to any part of the body elicits reflex contraction of appropriate muscle groups so that the part is moved away from the stimulus. For example, if a cat which has had the upper portion of the brain destroyed is suspended so that all four legs are hanging free, and a weak noxious stimulus is applied to a hind foot, it will cause reflex withdrawal of the paw by a movement at the ankle joint. A stronger stimulus will cause the leg to be

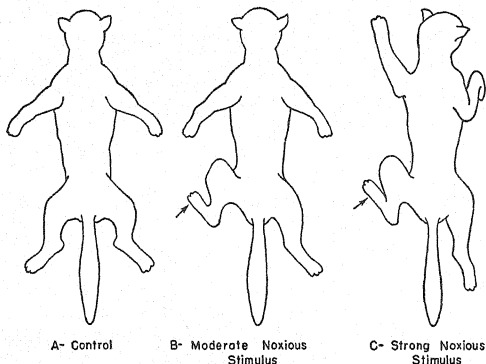


Figure 10-3. Reflex figures produced by application of a noxious stimulus to the left hindfoot of a cat.

(From Youmans' *Basic Medical Physiology*.)

withdrawn, flexion occurring at the ankle and knee, and the opposite hind leg may be slightly extended. A still stronger stimulus applied to the same foot will cause flexion of the leg at ankle, knee, and hip, extension of the opposite hind leg, extension of the foreleg on the same side, and flexion of the foreleg on the opposite side. Thus a complex *reflex figure* or pattern is produced by means of connections in the spinal cord. The response is purposeful in that the foot is removed from the damaging environment, and the animal assumes a position for walking away. It is apparent that the flexor reflex involves connections with many segments of the spinal cord and that some of the pathways cross in the cord to influence motor neurons on the opposite side.

Reciprocal innervation. When the flexor response occurs at a given joint on a reflex basis, as described above, the movement is accomplished not only by contraction of the flexor muscles, but also by relaxation of the extensor muscles, if the latter are under tonic influences at the time of the stimulus. Thus, a strong noxious stimulus may alter the status of contraction of most of the muscles in all four limbs and many of the trunk muscles as well. The inhibition of an extensor muscle during the

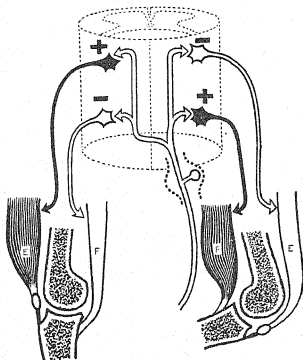


Figure 10-4. Diagram showing essential features of reciprocal innervation.

E = knee extensors; F = knee flexors; + = central excitation; - = central inhibition. Stimulation of afferent nerve shown on right elicits the pattern of response which is illustrated. (Reproduced by permission from Wright, *Applied Physiology*. Copyright, 1952, by Oxford University Press.)

contraction of the flexor muscle, or vice versa, is known as *reciprocal inhibition*, and flexor and extensor muscles are said to be reciprocally innervated. This is diagrammed in Figure 10-4. Nerve impulses arriving at some synapses cause inhibition, while at others the impulses cause excitation.

Degree and duration of reflex response. The reflex response in a given muscle differs from the response of the muscle to stimulation of its motor nerve in several respects. The latent period for the reflex response is longer, the contraction is slower and more prolonged, and the reflex contraction may persist for a brief time after cessation of the stimulation of

the afferent nerve. The great variation in degree of reflex response already has been described. The increase in reflex response which occurs as one increases the strength or duration of stimulation of afferent nerves is dependent upon summation. The afferent fibers diverge to supply several motor neurons and, on the other hand, afferent fibers converge upon some of the same motor neurons. When a given group of afferent nerve fibers is stimulated, a *pool* of motor neurons in the spinal cord is influenced. Some of these neurons are activated and conduct impulses, while the excitability of the other neurons in the pool is increased. The term used

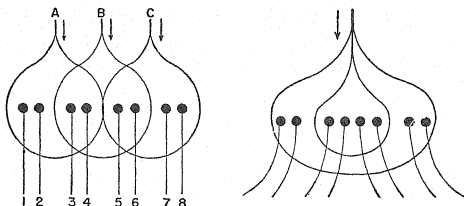


Figure 10-5. Diagram of some features of the reflex connections in the spinal cord.

On the *left* it is shown that an impulse entering by an afferent neuron, for example B, is distributed by branches so as to influence a number of neurons in the cord. Also, each neuron in the cord receives impulses from a number of neurons. This illustrates *divergence* and *convergence* in the reflex pathway. On the *right* the effect of a volley of impulses in an afferent nerve on neurons in the spinal cord is illustrated. The central group of four neurons is activated by the single volley; the four neurons in the outer circle are facilitated, but are not activated. (From Youmans' *Basic Medical Physiology*.)

for this subliminal excitation is *facilitation*. If two afferent pathways are stimulated simultaneously and there is convergence of these pathways upon some of the same motor neurons, there may be activation of certain neurons which were not activated by stimulation of either pathway alone. This result indicates that activity in each afferent pathway causes facilitation of certain neurons, so that, by spatial summation, these neurons can be activated when the two afferent pathways are stimulated simultaneously. The slower contraction of the muscle which is seen in reflex action occurs because there is asynchronous activation of the motor neurons. The process of summation to a level sufficient to produce a response takes longer at some neurons than at others. When the motor nerve is stimu-

lated, on the other hand, impulses are set up in all of the axons simultaneously, and they reach the muscle fibers almost synchronously.

The continuation of the reflex response for a brief interval following cessation of the stimulation is known as *after-discharge*. This also is related, in part, to the asynchronous activation of motor neurons; however, there are other more prominent factors. There are neuron circuits within the spinal cord and it seems probable that impulses may continue to "reverberate" in such circuits for a time after afferent impulses are no longer entering. Finally, due to the stretch reflexes there may be re-excitation of the motor neurons on a reflex basis. This latter influence can be eliminated by cutting appropriate dorsal roots.

Central reflex time. The time required for the impulse to pass through the part of the reflex arc that is located in the spinal cord or brain is the *central reflex time*. This is determined roughly by measuring the time from application of the stimulus until the time of response, which is the *total reflex time*, and subtracting from this the time required for the impulse to travel in the nerve fibers. The latter is calculated on the basis of measurement of the length of the fibers and knowledge of the rate of conduction in the fibers involved. The central reflex time varies with different reflexes and with the strength of the stimulus. For some reflexes it is as short as 3 milliseconds.

Reflexes show "fatigue" before there are any signs of fatigue on the motor side as determined by stimulation of the motor nerves. Since nerve fibers themselves are virtually indefatigable, it may be concluded that the altered reactivity has developed in the spinal cord and presumably at the synapse.

Allied and antagonistic reflexes. Two reflexes being elicited simultaneously may be *allied* or *antagonistic*. Allied reflexes are those which have similar influences on the final common path, that is, both promote excitation or inhibition, while antagonistic reflexes are those which have opposite influences on the final common path. For example, if the foot is pricked with a pin at the same time that the patellar tendon on the same side is tapped, the former stimulus will tend to cause flexion at the knee joint, and the latter will tend to cause extension. The two reflexes will compete to occupy the final common path and the response will be the resultant of the two opposite influences. The flexor reflexes typically are more successful in the competition for the final common path, hence they are said to be *prepotent*. Stretch reflexes are most easily counteracted when an antagonistic reflex is elicited.

Chapter 11

CUTANEOUS SENSES AND PROPRIOCEPTION

The senses commonly are divided into general and special. The special senses include sight, hearing, taste, olfaction, and the sense of position and motion. The receptors for the special senses are confined to relatively small areas in the retina, inner ear, dorsum of the tongue, and nasal mucosa. The general cutaneous (skin) senses include touch, cold, warmth, and pain. In addition there are various types of visceral sensation.

Cutaneous Senses

All portions of the skin are sensitive to changes in temperature and to touch and pain. The normal individual is capable of recognizing rather precisely the point on the skin that is the site of stimulation, hence the cutaneous senses are characterized by a well-developed *local sign*. Another striking fact about general cutaneous senses is evident if one carefully tests for sensitivity to cold, warmth, pain, and touch over a given portion of the skin. It is found that specific minute points show sensitivity, while small areas between these points are relatively insensitive. In other words, the cutaneous senses have a *punctate* distribution. The pain spots are more numerous in a given area than the spots which are sensitive to touch or to temperature.

In the case of *touch*, the effective stimulus depends upon deformation of the skin directly or by moving a hair. The sensation is tested for by means of a small camel's hair brush. Recognition of the location of a single spot being touched is called *tactile localization*, and the distance that the points of a compass must be separated in order for the subject to recognize that two points are being touched is known as *tactile dis-*

crimination. The latter is most highly developed at the finger tips, lips, and tongue where the compass points need be only two to three millimeters apart to be recognized as two points; while in the middle of the back the points touched must be six to seven centimeters apart. The effective stimulus for producing a sensation of *warmth* or *cold* is an increase above or decrease below the existing skin temperature. An exception to this is the paradoxical cold sensation; temperatures over 44°C. applied to cold spots give a sensation of cold. Cutaneous *pain* sense usually is tested by gently pricking the skin with a pin.

The fact that cutaneous senses can be elicited from specific "spots" rather than from every point on the skin, and the fact that several anatomically different types of receptors are present in the skin, would seem to fit with the theory of "specific nerve energies" which was advanced by Müller (1826). According to this view a given receptor or the afferent fiber which innervates it will give rise to the specific sensation subserved by it, and to no other, no matter what the nature of the stimulus. Müller's theory has the merit of being simple, but there are observations which are difficult to reconcile with it. For example, Weddell and associates have reported that certain areas of the skin which contain only naked nerve endings and basket endings around the base of hairs are sensitive to all forms of sensation. Therefore, they propose the hypothesis that recognition of a given sensation is brought about following the activation of a number of receptors more or less simultaneously and at a given frequency. Thus, low frequency discharge of a group of receptors, according to this hypothesis, could give rise to the sensation of touch and a higher frequency could cause sharp pain.

The afferent fibers carrying impulses from receptors enter the spinal cord by the dorsal roots and make connections for reflexes and with higher centers. The skin area innervated by a given dorsal root is known as a *dermatome*. These are illustrated in Figure 11-1. There is extensive overlap of the dermatomes, so that two or more adjacent dorsal roots must be sectioned before complete loss of cutaneous senses is produced in any skin area.

Pathways for cutaneous sensibility. The afferent fibers for pain, temperature, and part of touch enter the spinal cord to form synapses with cells in the posterior column of gray matter on the same side. See Figure 11-2. From these cells fibers pass across the cord to the opposite side to the spinothalamic tracts which are so named because they connect with the thalamus. The fibers for pain and temperature enter the lateral

(posterior) spinothalamic tract and the fibers for touch enter the ventral (anterior) spinothalamic tract. The fibers from this second neuron form synapses with the third neuron of the chain in nuclei in the thalamus, and, finally, fibers from these cells pass to Areas 3 and 1 of the cerebral

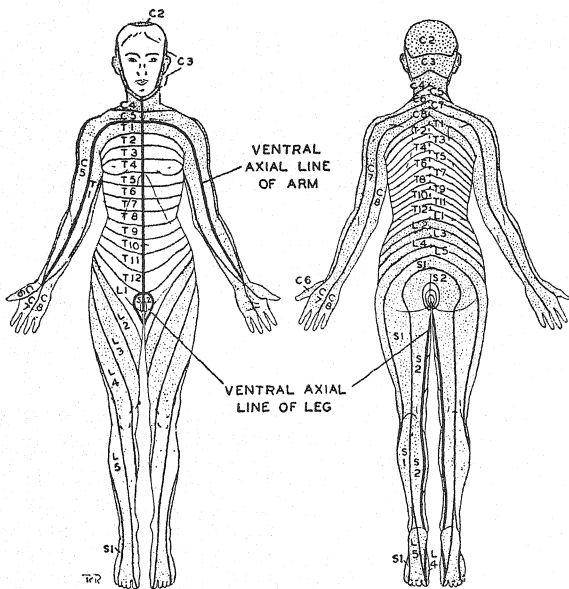


Figure 11-1. The dermatomes.

(Reproduced by permission from the original Figure 2, J. J. Keehan and F. D. Garrett, *Anat. Rec.*, 102:411, copyright 1948.)

cortex. These areas comprise the *sensory cortex* (Figure 11-6, page 127). Some of the touch fibers follow the same course as the pathway for conscious proprioception, which is described below. This is appropriate, since touch and proprioception are associated closely in the sense which is concerned with the recognition of size and weight of objects.

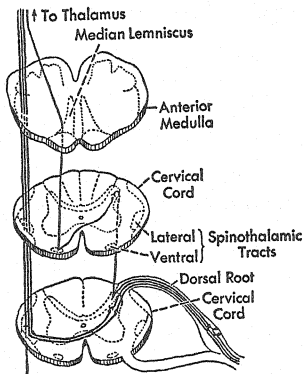


Figure 11-2. Diagram of pathways for pain and temperature and for part of the sense of touch.

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Proprioception

Proprioceptors include those receptors located in muscles, tendons, and joints which are activated by changes in length or tension of the muscle or the angle of the joint. Therefore, their activation provides information concerning the degree of activity in muscles and the position of the body.

There are three types of proprioceptors in muscles and tendons (Figure 11-3). In muscles, complex end organs called muscle spindles are located. The spindle contains a few muscle fibers of small diameter enclosed at one portion in a connective tissue capsule. These so-called *intrafusal* fibers are innervated by efferent nerves, known as fusimotor nerves, which are smaller in diameter than those which innervate the large fibers of the muscle itself. A large afferent nerve fiber forms an annulospiral ending around the midportion of the intrafusal fibers and a medium-size myelinated afferent fiber forms flower-spray endings on

the ends of the intrafusal muscle fibers. In tendons, there are diffuse branching terminations of afferent nerves (Golgi tendon organs).

Tension is exerted on the tendon, whether the muscle contracts in response to nerve impulses or is stretched passively by pulling on it, and the increase in tension causes impulses to be set up in the afferent fibers supplying the tendon organ. The receptors in the muscle spindles, like those of the tendon organs, also are activated during passive stretch, but may show a decreased rate of discharge when the muscle is activated by stimulation of its motor nerve. The explanation for this is that the spindle is arranged "in parallel" with the muscle fibers so that tension on the intrafusal fibers is reduced during muscular contraction produced by direct stimulation of the large-diameter axons of the motor nerves. If, however, the motor nerve to the muscle is stimulated with a strength of current great enough to activate the small efferent nerves to the intrafusal fibers, at the same time that it activates the large efferent nerves to the large fibers of the muscle proper, the tension in the intrafusal fibers will be increased and, consequently, the discharge rate in the afferent nerves coming from the muscle spindle will be increased.

The advantages of a receptor organ having the characteristics of the muscle spindle will become apparent in the consideration of control of movement. Such receptors do not appear to be suitable to subserve sensation of position or movement of a limb, but they do appear to be concerned with what has been called subconscious proprioception. Conscious proprioception, or kinesthetic sense—the sense of position and movement of the

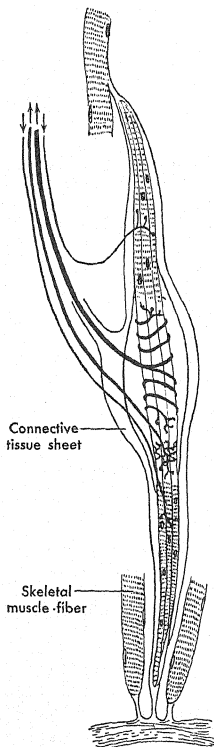


Figure 11-3. Innervation of muscle spindle.

parts of the body—probably is served mainly by the receptors in joints; and sense of tension on the muscle, which enters into judging the weight of an object being lifted, is dependent, in large part, on tendon organs.

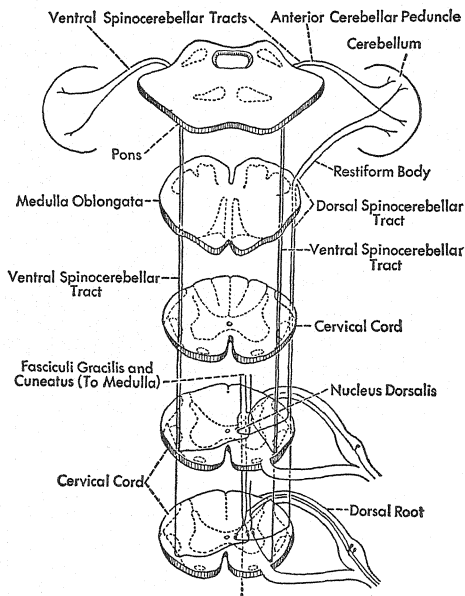


Figure 11-4. Diagram of pathways for subconscious proprioception.

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In Figures 11-4 and 11-5 the principal pathways for subconscious and conscious proprioception are illustrated. The former make connections with efferent pathways at subcortical levels and are concerned principally with the integration of muscular activity. The latter reach the cerebral cortex.

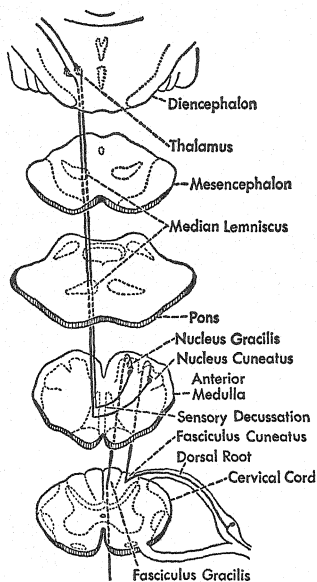


Figure 11-5. Diagram of pathways for conscious proprioception and for part of the sense of touch.

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The Thalamus and Sensory Cortex

The thalamus is an important relay station in the sensory system. All afferent impulses concerned with cutaneous senses and conscious proprioception are channeled into the thalamus, most of them directly, but also some indirectly from the cerebellum, and impulses are then transmitted to the sensory and motor areas of the cerebral cortex. Through the connections with the sensory cortex, one is aware of cold, warmth,

touch, and pain. The connections with the motor areas provide a mechanism for regulation of movement on the basis of information derived from the general senses.

The sensory cortex is located along the gyrus, just posterior to the central sulcus (Areas 3, 1, and 2 in Figure 11-6). The relation of this part of the brain to the general senses has been clearly established by several methods. First, after removal of the sensory cortex, the finer

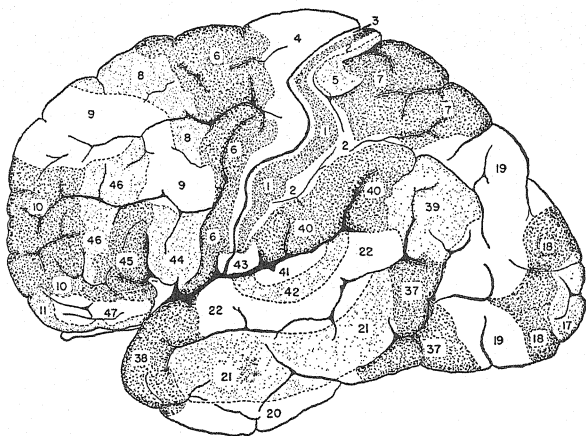


Figure 11-6. Areas of the cerebral cortex.

(After Brodmann.)

recognition of intensity of cutaneous stimuli is impaired; tactile localization and tactile discrimination are seriously impaired. Astereognosis is a particularly obvious manifestation of lesions of the sensory cortex. This refers to inability to identify an object by holding it in the hand and feeling its weight and contours. Second, evidence for representation of skin areas in the cerebral cortex is obtained by recording the electrical potentials in the cortex induced by stimulating the skin. When this technic is used, it is found that changes in potential are evoked in discrete areas in the sensory cortex when specific skin areas are stimulated by changes in

temperature or touch or pinprick. In other words, each part of the body is represented in a relatively small specific part of the cerebral cortex. The distribution of this representation along the postcentral gyrus of the monkey is illustrated in Figure 13-2 (S1).

Visceral pain. Impulses which give rise to visceral pain are carried to the central nervous system over small non-myelinated fibers which are found in the same gross nerves as the sympathetic or parasympathetic (visceral efferent) fibers. Axons from the second neurons of the pathway ascend in the lateral spinothalamic tracts of the same and opposite sides to reach the thalamus and finally the cortex. Pain from visceral organs commonly is "referred" to areas of the skin which are innervated from the same segment of the spinal cord that supplies afferent fibers to the involved organ. For example, pain from the diaphragm, which receives its afferent innervation from the fourth cervical segment, commonly is referred to the skin over the shoulder, since this skin area also has its afferent innervation from the fourth cervical segment. Another characteristic of visceral pain is that it is diffuse; thus, it is either poorly localized or actually incorrectly localized.

Chapter 12

MECHANISMS FOR CONTROL OF POSTURE

The muscles which act upon the skeleton to produce movement of parts of the body sometimes are called voluntary muscles. However, these muscles engage in a number of activities which are involuntary. Reflex responses, for example, are involuntary, and some of the considerably more complicated processes, such as posture, involve involuntary activation of skeletal muscle. Even when willed movements are being performed, automatic associated movements and adjustments of muscular tonus occur.

The maintenance of posture is accomplished by coordinated activity of many different muscles or groups of muscles, and at the same time the antagonists of these muscles are inhibited. The sustained activity in muscles which are engaged in the maintenance of posture is referred to as tonus and for the most part the muscles concerned are extensor in their action. In fact, the muscles which oppose the effects of gravity may be grouped together under the heading of "physiologic" extensor muscles even though a few of these, such as the muscles that prevent the jaw from dropping, are not extensor in an anatomic sense.

In considering posture, one is concerned first with the stretch reflexes in extensor muscles. When a person is in the standing position, the tension in the extensor muscles in the legs causes activation of receptors in the muscles and tendons and this results in continuous reflex excitation of the muscles. The reflexly induced tonus in the extensor muscles is the basic feature of posture. The degree of tonus in the extensor muscles is adjusted through influences from a number of sources including the proprioceptive pathways, the labyrinth of the inner ear, the retina, the cerebellum, and the cerebral cortex.

thine (vestibular) receptors. To study the *tonic neck reflexes* the labyrinth of the inner ear may be excluded by extirpation. The labyrinthectomized, blindfolded animal, when the head is passively flexed, assumes reflexly the proper attitude for looking under a shelf; the forelegs are flexed and the hind legs are extended. When the head is passively extended, the forelegs are extended and the hind legs are flexed so that the animal assumes the proper position for springing upward. When the head is turned to one side, the animal assumes the position for taking the first step to that side.

Role of Vestibular System

The internal ear is contained within the petrous bone of the skull and it consists of a bony or *osseous labyrinth* which is a series of continuous, characteristically-shaped cavities containing a *membranous labyrinth* (Figures 12-1 and 12-2). The membranous labyrinth is innervated by the two divisions of the VIIIth cranial nerve, the auditory, or cochlear, division, and the vestibular division. The auditory division innervates the cochlea which contains the end organs for reception of sound (page 166), and the vestibular division innervates the saccule, utricle, and the ampulla of each semicircular canal which contain the end organs for the

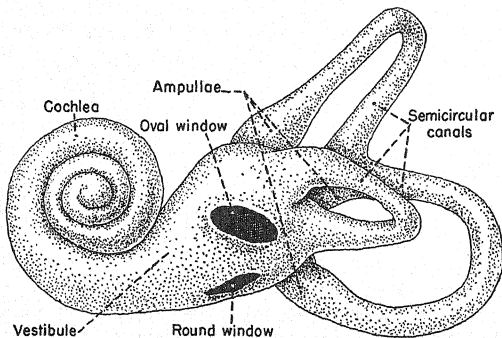


Figure 12-1. The osseous labyrinth.

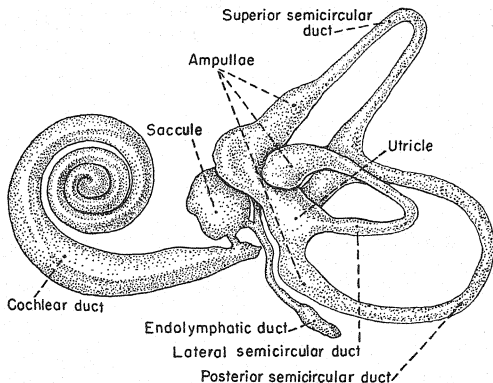


Figure 12-2. The membranous labyrinth.

sense of position and movement. In each labyrinth there are three semicircular canals arranged in planes at right angles to each other. One semicircular canal is in the horizontal plane when the head is tipped slightly forward, another canal is in a vertical plane which points laterally and anteriorly, and the third is in a vertical plane which points laterally and posteriorly at an angle of about 90° with the anterior semicircular canal. The ampullae are the bulbous ends of the canals located at the points of connection with the utricle. The membranous labyrinth contains fluid known as endolymph. The movement or weight of the fluid within the labyrinth serves to stimulate the end organs in the ampullae, saccule, and utricle, and this makes one aware of the position or direction of movement of the head when the eyes are closed. It is apparent that different patterns of stimulation are produced when the head is moved forward, backward, up, down, or is rotated in a clockwise or counterclockwise direction.

The three principal functions of the labyrinths and their connections are to influence postural activity in the eyes, trunk, and limbs, to guide the cerebellum in its regulation of muscular activity, and to provide conscious sensation of position and movement of the head. The labyrinth may be considered as a specialized organ of proprioception which supple-

ments the proprioceptive pathways in their functions. Since the vestibular system provides information similar to that obtained by vision and by proprioceptive pathways, the effects of bilateral labyrinthectomy in man are not prominent. The severity of the disturbances produced by bilateral labyrinthectomy is less, the higher the animal's place in the phylogenetic scale, while proprioception and vision become relatively more important.

Role of Cerebral Cortex

Certain exteroceptive and proprioceptive stimuli elicit reactions which serve to bring the feet into position for support of the body. These responses known as placing and hopping reactions are complex and they involve specific portions of the cerebral cortex. The following is an example of a *placing reaction*: A cat is held in air with head held up, or blindfolded, and with legs hanging free. The cat is moved horizontally so that the foreleg comes in contact with the edge of a table top. If the side of the leg contacts the table top, the leg is lifted and placed to the side and if the anterior aspect of the leg is contacted, the leg is lifted and placed forward; thus, the foot is brought up and placed on the top of the table. Once the sole of the foot comes in contact with a surface, the extensor thrust is elicited, and also the animal will execute voluntary movements of the legs in an attempt to gain its footing.

The *hopping reactions* are movements of the legs which help to maintain a standing position when the body is being displaced in the horizontal plane. For example, if a blindfolded cat is held so that it stands on one leg, movement of the body forward, backward, or laterally causes the animal to execute a series of hops in the direction of the displacement, so that the leg repeatedly is brought into a supportive position. These reactions in a given limb are eliminated by destruction of the areas of the cerebral cortex, the stimulation of which causes movement of that limb.

Chapter 13

MECHANISMS FOR VOLUNTARY MOVEMENTS

The use of skeletal muscle to perform willed or voluntary acts is an almost constant occurrence in the normal waking person. The neuro-anatomist and neurophysiologist knows rather precisely a number of different neurons and pathways within the nervous system which are utilized in the performance of volitional acts. These include two different groups of neuronal systems, commonly referred to as *pyramidal* and *extrapyramidal*, which conduct impulses from the cerebral cortex down through the brain stem and spinal cord, to influence the rate of discharge of motor neurons. The importance of the two systems and their general roles have been determined (as for other parts of the nervous system) mainly by observing the effects of stimulation or destruction by ablation in experimental animals or by disease processes in man.

Pyramidal and Extrapyramidal Systems

Certain areas of the cerebral cortex have been designated as motor areas on the basis of the fact that stimulation in these regions causes contraction of skeletal muscle, whereas stimulation of other cortical areas, with similar or somewhat stronger currents, does not cause movement. The main portions of the cortex from which movements can be elicited by electrical stimulation are shown in Figure 13-1. The central sulcus is just to the right of the region marked 4 gamma. The gyrus in front of this is the precentral gyrus and the one posterior to it is the postcentral gyrus. Thus the motor cortex includes some of the postcentral gyrus and extends forward about half of the distance to the frontal pole of the brain.

As shown, the motor cortex is composed mainly of Brodmann's areas 4, 6, and 8 (see Figures 11-6 and 13-1), but other areas also are included. The motor area also extends onto the part of the cortex which would be

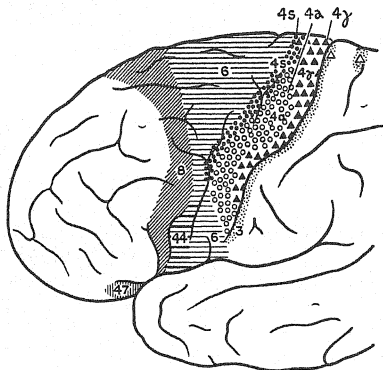


Figure 13-1. Diagram of the divisions of the precentral motor cortex.

Area 4 is divided into three zones, 4 gamma being the portion containing the Betz cells which give rise to fibers of the pyramidal tract. Both Area 4 and Area 6 contain neurons which give rise to fibers which belong to the extrapyramidal system. (By permission after Bucy, *Precentral Motor Cortex*. Copyright, 1944, by the University of Illinois Press.)

seen in a midsagittal section (as illustrated for a brain of a monkey in Figure 13-2).

Area 4 contains cell bodies of neurons which give rise to axons that pass down through the brain stem without interruption to form synapses on or near motor neurons in the brain stem and spinal cord. Some of the axons which descend from cell bodies of neurons in area 4 form synapses directly with the motor neurons, while others may make connections with the small neurons found adjacent to and innervating the motor neurons. The fibers which pass all of the way from the cortex to the vicinity of the motor neurons, without having a synapse interposed, are found together as a bundle in the part of the brain known as the pyramid (on each side), hence the name pyramidal tract. The general anatomical arrangement of the pyramidal tract is shown in Figure 13-3. It should be noted that most of the fibers cross to the opposite side of the body at the level of the medulla while some continue on the same side down into the spinal cord where they finally cross to form synapses with motor neurons.

Hence electrical stimulation of a point in area 4, using moderate intensity, elicits movements of specific parts on the opposite side of the body.

Each part of the body is represented in the motor area. Muscles of the head are represented in the lower portion of the precentral gyrus, then neck, arms, trunk, and legs are represented in turn. This order can be visualized roughly as the figure of a little person lying anterior to the central sulcus with feet toward the midline and head reaching to the lower end of the sulcus. The figure must be envisaged as being disproportionate in that the motor area representing the head and hands is quite large and that for the trunk and legs is relatively smaller. Recently, a second motor area which is smaller, but which contains representation for each part of the body, has been mapped in both man and lower primates (see Figure 13-2).



Figure 13-2. Primary and supplementary motor areas.

M I, primary motor area; M II, supplementary motor area. S I and S II indicate primary and supplementary sensory areas. These areas are shown as mapped on the brain of a monkey. The upper part of the figure is the sagittal section rotated up into view. (Courtesy of C. N. Woolsey.)

Neurons found throughout the cortical motor area (that is, both in and outside of area 4) give rise to axons which, unlike those of the pyramidal system, form synapses with other neurons deep in the brain. Impulses are relayed by second, third, or more neurons in the pathway at various

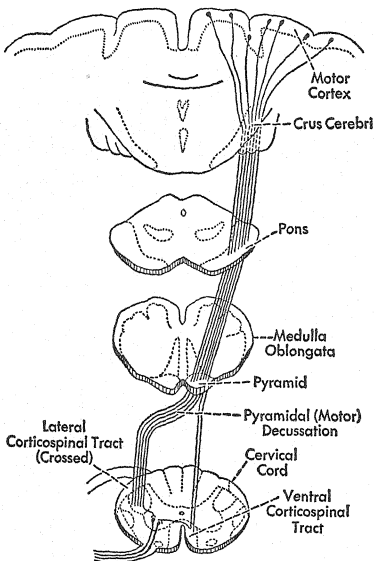


Figure 13-3. Diagram of the pyramidal system.

(Reproduced by permission from Walter and Sayles, *Biology of the Vertebrates*. Copyright, 1949, by The Macmillan Company.)

subcortical levels before reaching the cell bodies which give rise to the axons that pass down to the vicinity of the motor neurons. This less direct system of pathways concerned with control of activity of skeletal muscle is known as the extrapyramidal system.

It is known that volitional movements cannot be accomplished in a

normal manner if the motor areas or the pathways leading from them to the motor neurons are damaged. For example, in cerebral hemorrhage, or stroke, the pathways are damaged at a point deep in the brain and a characteristic change in control of muscular activity known as *hemiplegia* is produced. There is weakness and clumsiness in executing movements of the limbs on one side of the body. The abnormalities are on the side opposite the location of the hemorrhage in the brain. Also there is a stiffness or *spasticity* of the limbs which is related in part to hyperirritability of stretch reflexes.

In primates, ablation of area 4 initially causes paralysis on the opposite side of the body. Gradually, the animal shows considerable recovery, but there is residual impairment of the finer movements of the digits.

Section of the pyramids in monkeys results in diminished usage of the extremities on the side opposite to the lesion. The affected side engages in stereotyped activities (posture, locomotion), but use of the digits for discrete movements is lost. Recovery extends over a period of weeks, but defective control of finer movements persists.

Initiation and Coordination of Movement

When one performs a voluntary act he, of course, wills a movement and does not need to think about activating specific muscles. It is the pattern of movement that is willed and this is executed via the motor areas. Evidently, it is not willed in the motor areas. There is evidence that destruction of motor areas results in impairment of ability to perform the act but not in inability to will it. Just where willing of a voluntary act occurs is not clear.

Whenever a specific act is willed, a number of associated movements are necessary. If you reach to pick up a pencil, not only are the muscles of your hand and fingers utilized, but you turn your head, eyes, and trunk, and postural adjustments occur at the same time. Furthermore, as soon as muscles are brought into activity by an act of will the proprioceptive reflexes (page 122) are elicited and constitute a mechanism for regulating the smoothness of performance of the act. Impairment of the feedback over the afferent pathways from muscles and joints leads to clumsiness, or ataxia, and a tendency to overshoot or undershoot the mark.

It appears that the pyramidal tract is essential for finer control of muscles in the performance of willed acts, while the extrapyramidal

system, with its myriad connections, is utilized mainly in the production of the proper associated movements. This interpretation is indicated both by the anatomical characteristics of the two systems and the effects of lesions.

The *cerebellum*, through impulses received from the proprioceptive pathways, labyrinths, and other afferent systems (pages 125 and 132), plays an important part, both in the control of posture and equilibrium, and in the guiding of voluntary movement. Each cerebellar hemisphere receives proprioceptive and exteroceptive impulses from the same side of the body and from the labyrinth. Also, the cerebellum has efferent connections with a number of motor nuclei in the brain stem and with the thalamus and cerebral cortex; thus, it is interconnected with the extrapyramidal system. The cerebellum is concerned with modifying motor activities which are initiated elsewhere, hence impairment of its functions is manifested by disturbances in motor functions rather than abolition of motor functions. The clumsiness, coarse tremor, drunken gait, and other characteristic alterations in motor functions seen in patients with lesions of the cerebellum are referred to collectively as *cerebellar ataxia*.

Chapter 14

PHYSIOLOGY OF VISION

Physiological Anatomy of the Eye

The eyeball is a globe consisting of transparent media surrounded by three coats. The outer sclerotic coat, or *sclera*, forms the white of the eye and is composed of keratin, which, being tough and resistant, affords protection. The middle coat, or *choroid*, contains the blood vessels and hence is important for the nourishment of the eye. The inner coat is the *retina*, which contains the end organs and other portions of the nervous mecha-

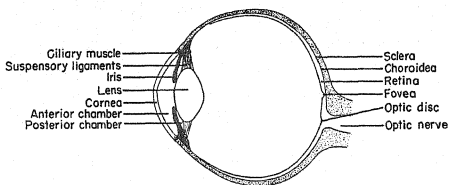


Figure 14-1. Section through the eye in the plane including the fovea and optic disk.

nism concerned with the sense of sight. In the anterior part of the eye, the sclera is modified into the transparent *cornea*. In a transverse section of the eye, it can be seen that the interior is divided into two chambers, *anterior* and *posterior*, by the *iris* and *crystallin lens*. The iris, which surrounds the pupil, contains radial and circular layers of smooth muscle. Contraction of the radial muscle produces enlargement of the pupil and contraction of the circular muscle produces constriction. The anterior chamber contains *aqueous humor* which constantly is being drained and re-formed. The posterior chamber contains a jelly-like substance, the

vitreous humor which is a permanent part of the eye. Light which enters the eye passes consecutively through the cornea, aqueous humor, lens, and vitreous humor to reach the retina.

The Eye as an Optical Instrument

An essential condition for seeing an object clearly is that all rays of light which diverge from any given point on the object be focused at a single point on the retina. The refraction of light by the eye may be illustrated by the focusing of a real image by means of a convex lens as shown in Figure 14-2. If A_0B_0 is an illuminated object, one can depict any num-

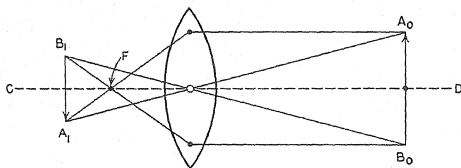


Figure 14-2. Formation of an image by a convex lens.

A_0B_0 is the object and A_1B_1 is the image formed. F is the principal focus for the convex lens; parallel rays entering the lens from A_0 and B_0 are crossed at this point. The rays from A_0 to A_1 and from B_0 to B_1 pass through the optical center of the lens, hence they are not refracted.

ber of rays of light diverging from any point on it. To construct the image produced by the lens, however, one needs to use only two rays coming from A_0 at one end of the object and two from B_0 at the other end. The straight line from A_0 to A_1 is drawn through what is known as the optical center, or *nodal point*, of the convex lens. Any ray which passes through this point, regardless of its direction, is not refracted. It will be noted that another ray is drawn from B_0 to B_1 through the nodal point. Now, if rays are drawn from A_0 and B_0 parallel to line CD (which passes through the midpoint of A_0B_0 and through the nodal point of the lens), these two rays will be converged, or focused, to cross CD at a point indicated by F . The distance from the nodal point of the lens to the focus F , known as the *focal length* of the lens, is shorter, the thicker the convex lens. It may be observed from the drawing, that if the refracted parallel

rays are continued on through the focal point, the upper one of the two rays will cross A_0A_1 at A_1 , and the lower one of the rays will cross B_0B_1 at B_1 . Hence the point of crossing of all rays which diverge from A_0 and pass through the lens is at A_1 , and likewise all rays which diverge from B_0 to enter the lens will be focused at B_1 . If a screen is placed at the plane in which A_1B_1 is located, a small inverted real image will be seen. In the case of the eye, the cornea and crystalline lens may be considered

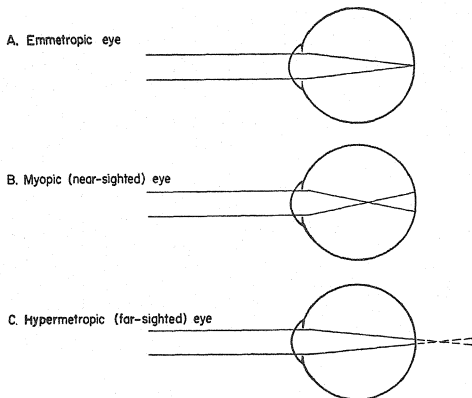


Figure 14-3. Effects on parallel rays entering unaccommodated normal (emmetropic) eye (A), myopic eye (B) and hypermetropic eye (C).

(From Youmans' *Basic Medical Physiology*.)

to act as a single convex lens and the screen is the retina. Objects in the field of vision are focused on the retina in an inverted and reversed position.

As light passes from one medium to another, if the media are of different density and the rays are not perpendicular to the interfaces of the two media, the rays will be refracted. The ray can be visualized as being bent into the more dense medium. Water and glass, for example, are more dense than air. The two major types of spherical lenses are convex and concave; the convex lens is characterized by being thicker at the center than at the periphery, and the concave lens is thinner at the

center than at the periphery. A convex lens converges parallel light rays and a concave lens causes divergence of such rays.

The strength of a lens is expressed in diopters. This is the reciprocal of the focal length in meters. For example, if a convex lens brings parallel rays to a point focus at a distance of one meter it is a $+1D$ lens, at one-half meter a $+2D$ lens, and at two meters a $+\frac{1}{2}D$ lens. Concave lenses have a virtual focus on the same side of the lens as the entering rays and are designated by a minus sign. The virtual focus is located by extending backwards through the lens the lines coinciding with the refracted rays. The strength of a system of lenses equals the algebraic sum of the individual lenses. Thus, a $-1D$ lens will neutralize the effect of a $+1D$ lens.

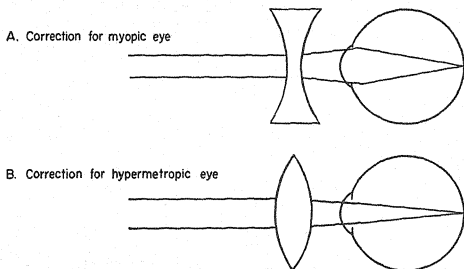


Figure 14-4. Correction for myopia and hypermetropia.

In myopia a concave lens is used to create divergence of rays of a degree such that the unaccommodated eye will bring the rays to a focus on the retina. In hypermetropia a convex lens is interposed to cause convergence of the parallel rays so that the unaccommodated eye will bring them to a focus on the retina. (From Youmans' *Basic Medical Physiology*.)

The compound optical system of the eye can be simplified to a *reduced schematic eye*. The concept of the reduced schematic eye can be used, in modified form, to illustrate the handling of light rays by the eye. A circle is drawn to represent the eye, then a point is arbitrarily established to represent the nodal point of the reduced schematic eye. Rays entering the eye and passing through the nodal point are not refracted; other rays are shown as being refracted where they strike the plane which includes the nodal point and lies at right angles to the visual axis. The latter is a straight line established by the nodal point of the eye and the fovea.

A normal, or *emmetropic* eye, is one having a refracting system of strength, such that parallel rays entering it are brought to focus at a point on the retina when the eye is in the relaxed, i.e., unaccommodated, state. Eyes which fail to do this are classed as *ametropic*. When an unaccommodated eye brings parallel rays to a focus in front of the retina, it is said to be *myopic*, or nearsighted, and when the point of focus is in back of the retina, the eye is *hypermetropic*, or farsighted.

The correction for an ametropic eye is a lens of strength and sign, such that the lens and the refracting system of the relaxed eye together will cause parallel rays to be brought to a point focus on the retina. A convex lens is required to correct hypermetropia and a concave lens is needed for myopia.

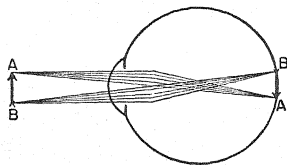


Figure 14-5. Conditions for clear vision.

Rays diverging from a point on the object are converged to a point on the retina.
(From Youmans' *Basic Medical Physiology*.)

In *astigmatism*, the refracting system is not of equal strength in all meridians. Commonly, it is strongest in a meridian at right angles to the meridian in which the refraction is weakest. The correcting lens must be cylindrical, that is, of greater strength in one meridian than in another meridian at right angles to the first. An astigmatic eye may also have various degrees of either myopia or hypermetropia.

Since the essential condition for clear vision is that rays of light diverging from each point on an object are refracted, so as to be brought to a point focus on the retina, the emmetropic eye must undergo an increase in refractive power (namely, accommodate; page 148) to see an object, and the degree of accommodation must be greater, the nearer the object. The uncorrected hypermetropic eye must accommodate even more than the emmetropic eye, in order to bring diverging rays to a focus on the retina. The relaxed myopic eye, on the other hand, is in focus for a certain plane, and this plane is closer to the eye, the greater the degree of

myopia. Objects at this plane are seen clearly by the myopic eye without accommodation; objects closer than this require accommodation and objects which are farther away cannot be seen clearly without a concave correcting lens.

Binocular Vision and Fusion

Binocular vision is defined as the coordinated use of the two eyes to produce a single mental impression. It serves to minimize optical defects in one eye and provides for perception of depth and distance. The latter

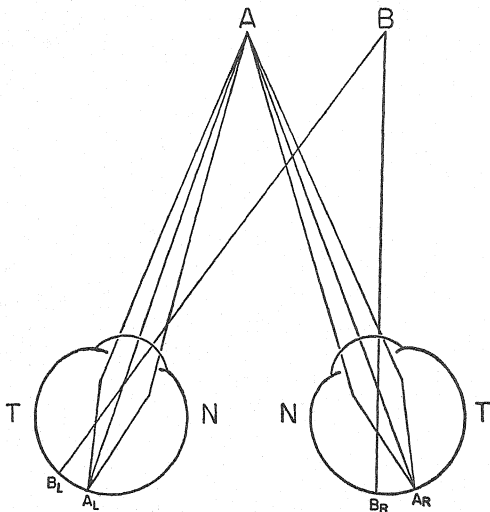


Figure 14-6. Conditions for binocular vision.

T, temporal; N, nasal; R, right; L, left. Eyes have fixed point A and are in focus for this point. Lines A-A_L and A-A_R include the point of fixation, the nodal point, and the fovea of the corresponding eye. Rays from B are focused on the temporal side of the fovea of the left eye and on the nasal side of the fovea of the right eye. (From Youmans' *Basic Medical Physiology*.)

is known as *stereoscopic* vision. An anatomical requirement for binocular vision is that parts of the visual fields overlap. In some vertebrate animals, there is no overlap of the two visual fields and in others the overlap is quite small. The greatest overlap occurs in primates, in which case the visual axes are parallel in the resting state. For binocular vision to occur, similar images must be focused on the two retinae, and, furthermore, these must be formed upon physiologically corresponding points, namely, on the nasal half of one retina and the temporal half of the other. In man, when the refracting systems of the two eyes are similar and the visual axis of each eye is in line with the object, these essential conditions for binocular vision are established. When an object becomes focused on retinal areas which do not correspond, if it attracts attention, adjustments of the extraocular muscles occur, so that the images immediately are shifted to corresponding retinal areas. This automatic process is known as *fusion*.

Fixation and Accommodation

When an object enters the field of vision and attracts attention, three processes occur virtually simultaneously: fixation, fusion, and accommodation. *Fixation* is the lining up of the eye, so that a point in the field of vision, the nodal point of the eye, and the fovea of the retina lie in a straight line. Fusion, as already described, refers to the alignment of the two eyes with reference to the same point in the field of vision, so that homologous portions of the retinae are stimulated. *Accommodation* proper refers to the adjustments of the eye by which objects at different distances from it are seen clearly. By reference to Figure 14-7 it may be seen that the nearer an object is brought to the eye, the more divergent are the rays which come from the object to enter the transparent media of the eye. Since the essential condition for clear vision is that the rays diverging from a point on the object be brought to a point focus on the retina, more bending of the rays is required when the object is closer to the eye. In order that more convergence of rays will occur, it is necessary for the crystalline lens to thicken. This is accomplished by contraction of the ciliary muscle which releases tension on the suspensory ligament of the lens and allows it to thicken of its own elasticity. A second feature of accommodation is that the pupil constricts. The advantage of this is related to the fact that rays which enter the periphery of the crystalline

lens are not focused at exactly the same point as rays which enter near the nodal point. This is a characteristic of spherical lenses which is known as *spherical aberration*. When the pupil constricts, the peripheral rays are prevented from entering and the remaining central rays may be more sharply focused. It should be recognized that, if a brightly illuminated object is moved closer and closer to the eye, the constriction of the pupil is produced, not only as a part of the accommodation mechanism,

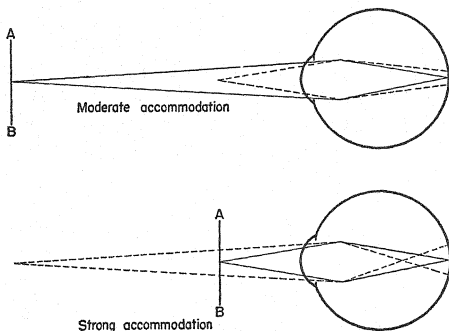


Figure 14-7. Accommodation.

Above: the eye is accommodated for plane AB. Rays diverging from a point closer than this, as shown by the broken lines, are not refracted sufficiently to be focused on the retina. *Below:* the eye is accommodated sufficiently to bring to a focus on the retina, rays diverging from a point on plane AB. Rays diverging from a point at a greater distance are crossed in front of the retina. (From Youmans' *Basic Medical Physiology*.)

but also because of the light reflex which is described below. A third feature of accommodation is the greater convergence of the optical axes of the two eyes which is necessary to maintain fusion as the object is brought closer. That this would be necessary is evident from study of Figure 14-6.

The accommodation "reflex" is a relatively complex response dependent on cortical centers. Unlike the light reflex, it requires consciousness, and it utilizes pathways to and from the "visual" cortex. Fixation also requires attention in a conscious subject and involves pathways similar to those required for accommodation.

As an object is brought closer and closer to the eye, the degree of accommodation progressively increases until a maximum is reached at the *near point*. If the object is brought any closer than the near point, it cannot be seen clearly because of inadequate refraction. The near point is at about 7 cm. in front of the eye in early life and recedes steadily with age until it reaches about 40 cm. as the crystalline lens gradually loses its elasticity. The recession of the near point with age is known as *presbyopia*. Near objects can be seen clearly only by the aid of convex lenses. The *range of accommodation* is the increase in refractive power from that required for viewing an object at an infinite distance to that which is achieved when the object is at the near point. This varies from about 14 diopters in children to about 2 diopters in individuals beyond 55 years of age.

The Light Reflex

The constriction of the pupil which is elicited by shining light into the eye is known as the *light reflex*. The constriction of the pupil occurs on both sides, even though the illumination is increased on one side only. The response on the illuminated side is the *direct* light reflex and that on the opposite side is the *consensual* light reflex.

The afferent fibers for the light reflex are in the optic nerve (IIrd cranial nerve); some of the fibers cross to the opposite side in the optic chiasm and others cross to the opposite side in the brain stem. The oculomotor nuclei (IIIrd cranial nerve) of both sides receive connections from each retina. Efferent fibers for the reflex are in the long ciliary nerve which connects with the ciliary ganglion, and postganglionic fibers pass from the ciliary ganglion to the circular muscle of the iris. The efferent pathway is a part of the cranial portion of the parasympathetic system.

Pupillodilator Reflexes

The radial muscle of the iris, which on contraction produces dilatation of the pupil, has an excitatory innervation from the sympathetic system. Smooth muscle fibers in the upper and lower eyelids, in the nictitating membrane, and in the soft tissues in back of the eye also have a similar innervation. Preganglionic fibers come from the upper thoracic segments

of the spinal cord and form synapses with cell bodies in the superior cervical ganglion; postganglionic fibers pass from this ganglion up along the branches of the arterial tree to reach the smooth muscle. Stimulation of the cervical sympathetic trunk or physiological activation of the sympathoadrenal system causes pupillary dilatation.

Neural Pathways for Vision

When light reaches the retina, receptors—the rods and cones—are stimulated and impulses are carried by neural pathways back to the cortex of the occipital lobe. Nerve fibers pass from ganglion cells of the inner layer of the retina and converge to form the optic nerve. The point of convergence of the fibers forms the optic nerve head which contains no receptors and constitutes the blind spot. The *fovea centralis* is the portion of the retina which normally becomes directly aligned with the nodal point of the eye and with the object toward which the gaze is directed. The fovea is in the center of a small area of the retina called the *macula lutea* (yellow spot). The nerve head is 15° to the nasal side of the fovea and consequently, the visual defect is 15° to the left of the optical axis (see below).

To understand the pathways for vision, it is necessary to think of each retina and the visual field of each eye as being divided into a nasal and a temporal half by the vertical plane in which the visual axis lies. Rays of light which enter the eye from points located in the nasal half of the visual field impinge upon the temporal half of the retina, and light entering from the temporal half of the visual field strikes the nasal half of the retina. The representation on the retina of any point in the visual field may be established by drawing a straight line from the point in the visual field through the nodal point of the eye to the retina. From these facts, it is apparent that loss of sensitivity of a portion of the retina on the nasal side would produce a defect in the temporal portion of the field of vision, and damage to the temporal portion of the retina would produce a defect in the nasal portion of the visual field.

The two optic nerves pass back and medially to form a cross, the *optic chiasm*, which is located just in front of the pituitary gland. As illustrated in Figure 14-8, fibers from the temporal halves of the retinae swing laterally to make connections with neurons, in a structure called the lateral geniculate body, on the same side, while fibers from the nasal

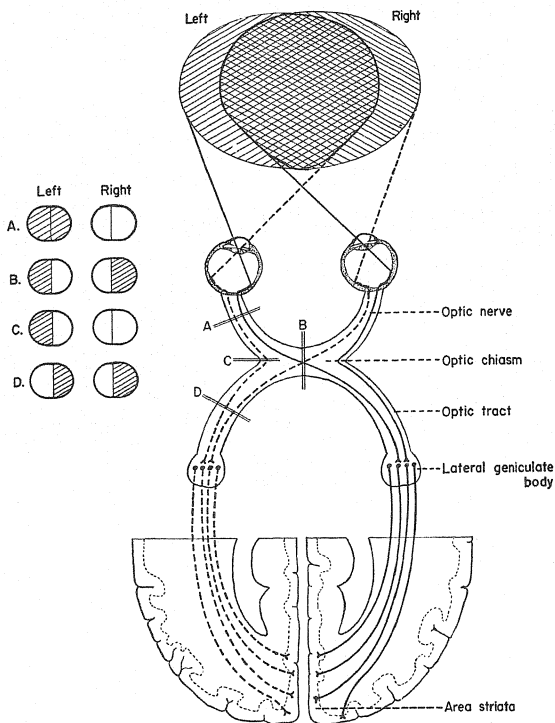


Figure 14-8. Diagram of the neural pathways for vision.

Effects on the visual fields for each eye produced by lesions at points in the pathways indicated by A, B, C and D are illustrated in the correspondingly lettered drawings on the left. The portion of the visual field which is lost in each case is filled in with diagonal lines. (From Youmans' *Basic Medical Physiology*.)

half of each retina cross in the optic chiasm to the opposite side to connect with the lateral geniculate body. Impulses are relayed from the geniculate bodies to the occipital cortex of the same side. It may be seen by studying Figure 14-8 that the left half of each retina, and hence the right half of the visual field of each eye, is represented in the left occipital cortex, and the left half of the visual field is represented in the right occipital cortex. The effects of lesions of the neural pathway for vision also are illustrated in the figure.

The optic tract has two major sets of connections; fibers make connections with the efferent pathway for the light reflex, and the visual pathway conveys impulses to the primary cortical visual area in man. Only the latter connections are shown in Figure 14-8. The visual area corresponds to area 17 of Brodmann (Figure 11-6), which lies along the lips of the calcarine fissure on the medial and cerebellar surfaces of the occipital lobe. The term *area striata*, which is applied to this portion of the cortex, is derived from its histological characteristics. Area 17 is the sole recipient of optic radiations from the geniculate bodies and there is definite localization of the retinal representation. Lesions of the occipital cortex may produce loss of the opposite half of the visual field of each eye, except that the macula is spared, possibly because of bilateral representation.

Control of Eye Movements

There are three major groups of ocular movements: (1) voluntary movements, which include the parallel movements occurring when the direction of the gaze is changed by an act of will, (2) the fusion response described on page 146, and (3) the reflex movements elicited from changes in the position of the head and originating largely from the labyrinths (page 132). The muscles of the two eyes work together in different combinations, according to which mechanism activates them. Six extraocular muscles are connected with each eyeball. These are shown in Figure 14-9. (1) The *lateral rectus* directs the eye to the temporal side; (2) the *medial rectus* directs it to the nasal side; (3) the *inferior oblique* directs it upward and outward; (4) the *superior oblique* directs it downward and outward; (5) the *superior rectus* directs it upward and inward; and (6) the *inferior rectus* directs it downward and inward. The lateral rectus muscle is innervated by the abducens (VIth cranial) nerve, and

the superior oblique by the trochlear (IVth cranial) nerve. The remaining four extraocular muscles and the levator of the upper eyelid are innervated by the oculomotor (IIIrd cranial) nerve. The oculomotor nucleus, which gives rise to the axons of the IIIrd nerve, consists of several groups of cells located in the gray matter of the upper part of the midbrain ventral to the aqueduct of Sylvius.

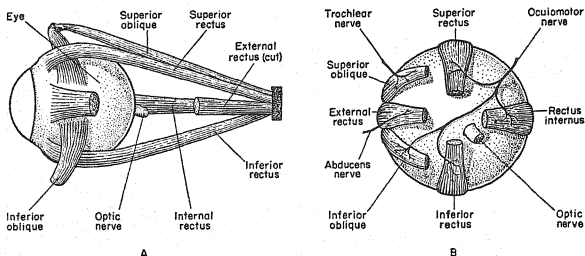


Figure 14-9. Extraocular muscles of the left eyeball.

A, side view; B, posterior view. (By permission, after Neal and Rand, *Comparative Anatomy*. Copyright, 1936, by The Blakiston Co. After Warren and Carmichael.)

Physiology of the Retina

The sense of vision in man includes the recognition of outlines and details of objects, appreciation of illumination and color, and appreciation of depth and perspective. The receptors concerned are the rods and cones located in the retina. In Figure 14-10 the distribution of the neural elements in the retina is shown in simplified form. The cones are concentrated in and around the macula lutea, which is the most sensitive part of the retina. The cones decrease in number toward the periphery of the retina, while the rods are least concentrated in the macula and increase in number toward the periphery.

Duplicity theory of vision. The cones are concerned with perception of detail and color and are relatively insensitive to light, while the rods, through a process known as *dark-adaptation*, are highly sensitive to light. The vision which is dependent on the cones, occurring primarily in the

light-adapted eye, is known as *photopic* vision, and that of the rods, or dark-adapted eye, is *scotopic* vision.

Depth perception. Perception of depth depends upon the cone system and upon binocular vision. When an object is viewed by the two eyes, the

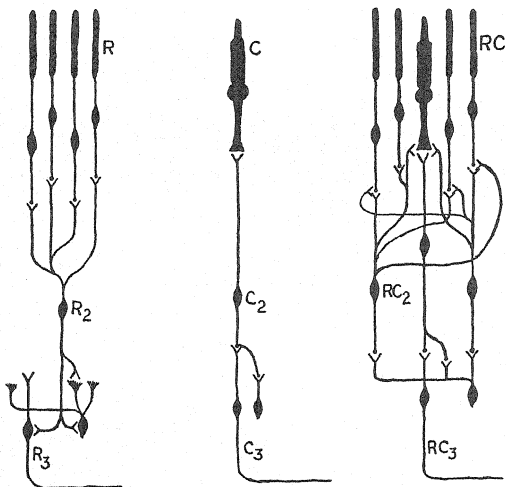


Figure 14-10. Typical arrangements of neural elements in the retina.

R—rods. R_2 —second order neurone linking impulses from a group of rods. R_3 —third order neurone conveying impulses from rod to brain. C—cone. C_2 —second and third order neurones conveying impulses from single cone. RC—mixed group of rods and a cone. RC_2 —second order neurones linking impulses from the mixed group. RC_3 —third order neurone conveying impulses from the mixed group to the brain. (Other neurones effecting a back-linkage have been omitted.) (Reproduced by permission from Lee, *Physiology of Tissues and Organs*. Copyright, 1950, by Charles C Thomas.)

images falling on the two retinae are not identical. The difference is shown if the object is photographed from the position of each eye, and the difference is greater, the closer the object is to the eyes. If the two pictures, which have been photographed, are arranged, so that each is

seen only by the appropriate eye, one gets the same impression of depth that is obtained by actually viewing the object.

Dark-adaptation. Everyone has experienced the inability to see for a few minutes, after walking from the bright outdoors into a relatively dark room; then, within a few minutes, vision in the dim light improves. The process by means of which the retina becomes more sensitive in dim light

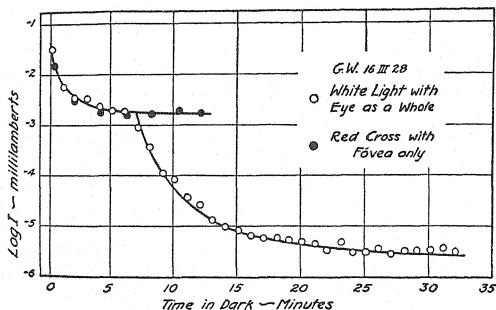
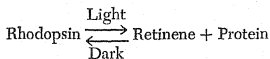


Figure 14-11. Rate of dark-adaptation in rods and cones.

Curve is obtained by plotting the visual threshold against time spent in darkness. Results of testing with white light are indicated by the open circles. The lowering of the curve indicates less brightness required to attain the visual threshold. The initial curve for the adaptation to white light is due to adaptation in the cones and the next portion is due to adaptation in the rods. To obtain a curve from the cones only, shown in solid circles, stimulation of the rods was avoided by using red light and foveal fixation. (Reproduced by permission from Hecht, *A Handbook of General Experimental Psychology*, C. Murchison, Ed. Copyright, 1934, by Clark University Press.)

is known as *dark-adaptation*. Conversely, a loss of sensitivity to light occurs during a few minutes on exposure of the eye to bright light; this is known as *light-adaptation*. The rate of occurrence of dark-adaptation can be measured by determining at frequent intervals the minimum amount of light that can be detected by the eye. The curve obtained is shown in Figure 14-11. It is seen that the cones dark-adapt first, but show a relatively small degree of increased sensitivity. The rods adapt later; however, they show a much greater increase in sensitivity. In the figure, it is shown that dark-adaptation is almost complete within 15 minutes, but continues very slowly for a considerably longer period.

The basis for dark-adaptation is a chemical reaction involving a retinal pigment known as *rhodopsin*, or visual purple. When rhodopsin is exposed to light, it is bleached to *retinene*, or visual yellow, and the retina becomes less sensitive to light. In the dark, retinene is converted back to rhodopsin and sensitivity to light is regained. These reversible reactions are as follows:



Rhodopsin is a protein combined with a color-bearing, or chromophore, group. Light causes a breakdown of this combination, releasing retinene. The latter compound has been shown to be a derivative of vitamin A. Severe deficiency of vitamin A causes night blindness, since the retina cannot produce adequate amounts of visual purple.

Color vision. To understand color vision, one must know certain elementary facts about the nature of light. Light is propagated as waves, and white light is composed of waves of different lengths within the range from 39×10^{-6} cm. to 78×10^{-6} cm. These waves, which are capable of stimulating the retina, represent a small fraction of the complete *electromagnetic spectrum*. The waves in this spectrum which are shorter than the waves in the visible portion and are next below it are the ultraviolet rays, and next below the ultraviolet are the X rays. The next longer wave lengths above the light rays are the infrared, or heat, waves.

When a beam of white light is allowed to enter a prism, the different wave lengths which make up the white light are refracted to different degrees. The longer the wave length, the less is the degree of refraction. Thus, the wave lengths are separated out and each is seen as a single color. The colors, consecutively, from those caused by the longest wave lengths to those caused by the shortest, are red, orange, yellow, green, blue, indigo, and violet.

From the facts which have been presented above, it is apparent that all retinal elements capable of responding to any single wave length can be activated simultaneously by white light, since such light contains virtually all wave lengths that can stimulate the receptors in the retina. A single wave length on reaching the retina is seen as the color which this wave length produces on a screen when it is separated out by means of a prism. Although a single wave length gives rise to recognition of a given color, it is possible to elicit the same color sensation by mixing two or three different colors. In fact, any color can be produced by mixing the three

primary colors, red, green, and blue, in suitable proportions. In actual practice, this is done by means of three disks each of which has a hole in the center and a slit along a radius, so that the disks can be put together and overlapped by any desired amount. Then the three overlapping disks are fastened to an axle which is turned rapidly by an electric motor. The whirling of the disks fuses the three colors into one.

To explain the fact that any color sensation can be produced by mixing of red, green, and blue, it has been postulated that there are three color-sensitive mechanisms in the retina contained, perhaps, in three different

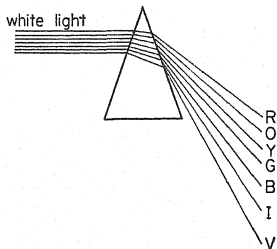


Figure 14-12. Diagram of effect of prism on white light.

types of cones. One of these mechanisms is considered to respond maximally to blue, another to green, and the other to red, although it is believed that each mechanism responds in lesser degree to each of the other two colors. Any color will stimulate the three different mechanisms in a characteristic proportion and hence give rise to the sensation of that particular color. This is the *Young-Helmholz theory* of color vision. The theory also serves to explain the different types of *color blindness*. Most commonly, reds and greens are confused, and the explanation for this, according to the Young-Helmholz theory, is that either the red or green color-perception mechanism is poorly developed or absent. In such cases, all colors that the subject can distinguish can be matched by mixtures of two primary colors instead of three, and the subject is said to have *dichromatic* color vision rather than *trichromatic*, as in the normal person.

Visual acuity. Visual acuity is measured by bringing two points or parallel lines, at a given distance from the eye, closer and closer together until the eye is just unable to distinguish the separate points. The angle

that is produced by straight lines drawn from the two points through the nodal point of the eye is the visual angle. In actual practice, visual acuity can be tested by means of a broken circle printed on a card. The examiner moves the card farther and farther from the subject until he can no longer detect the gap in the circle. Normally, the visual angle is near one minute, when neither illumination of the test object nor contrast between it and its background are limiting factors. Visual acuity is greatest when the pupil is moderately constricted, since pupillary constriction minimizes spherical and chromatic aberration. Also, visual acuity is greatest for light of a single wave length, since, in this case, chromatic aberration is completely avoided. Visual acuity is greatest in the fovea and decreases from the fovea toward the periphery of the retina.

Chapter 15

PHYSIOLOGY OF HEARING. TASTE AND OLFACTION

Hearing is produced when vibrations of a medium, normally air, are transmitted to the inner ear. The vibrations must be within a certain frequency range and must be of sufficient amplitude to produce the sensation of hearing. The audible range of frequencies for man is from 16 to 20,000 waves per second, but some animals, such as the bat, can hear considerably higher frequencies.

Characteristics of Sound Waves

When the prong of a tuning fork is set in motion, it alternately produces pressure and rarefaction of the air adjacent to it, and this causes back-and-forth movement of the air molecules at the same rate. The vibrations, or waves, are propagated through the air at a speed of 1087 feet per second. In water, sound waves travel 4714 feet per second. The type of movement shown by the vibrating prong of a tuning fork is known as *simple harmonic motion*, which may be exemplified by the projection of uniform circular motion in the plane of the circle which it describes. Thus, if an illuminated spot is moving in a circle at a uniform speed and a strip of film is allowed to move in the plane at right angles to the circle being described, the line recorded on the film will be a graph of simple harmonic motion. The symmetrical wave described is known as a sine wave. This is illustrated in Figure 15-1. *Frequency* of sound waves refers to the number of round trips, or complete vibrations, made by the vibrating particle per unit of time. *Amplitude* refers to the amount of displacement of a vibrating particle from the mean position; it is one-half the distance through which the particle moves.

When one vibrating body is coupled with another body, either by gas, liquid, or solid, the latter body is forced to vibrate at the same frequency as the former. If the vibrations of the forced body cease rapidly, following cessation of vibration of the forcing vibrator, the body is said to be highly *damped*, and if the forced body fails to pass the point of rest following removal of the forcing vibrations, the body is critically damped.

The vibrations which reach the ear under ordinary circumstances are not simple waves. They are quite irregular, but they can be described in terms of two or more simple waves. When waves of differing frequency are produced, they will be in phase and hence reinforce each other in each second a number of times which is equal to the difference in their frequencies. This is the basis for *beats*. The *pitch* of the sound is related to the frequency of the main wave, or fundamental.

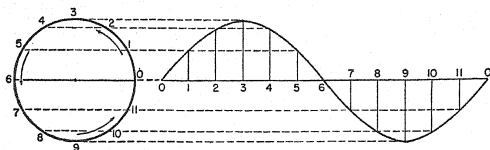


Figure 15-1. Simple harmonic motion.

Shape of tracing obtained when uniform circular motion of a point of light is recorded on film moving at a constant speed in a plane at right angles to the circle being described. (From Youmans' *Basic Medical Physiology*.)

The *intensity* of sound, which is directly related to the amplitude of the vibrations, is expressed in *bels*. The decibel is one-tenth of a bel. The wave power for two bels is 10 times that for one bel, and the wave power for three bels is 100 times that for one bel, etc.

Physiological Anatomy of the Ear

Anatomically, the ear is divided into three parts: external, middle, and internal (Figure 15-2). The external ear includes the pinna and the external auditory canal, the middle ear includes a cavity filled with air and containing three small auditory ossicles, and the inner ear is the labyrinth which consists of the semicircular canals and ampullae, innervated by the vestibular division of the VIIIth cranial nerve, and the cochlea, innervated

by the auditory division of the VIIIth nerve. The functions of the semi-circular canals already have been described (page 133).

The pinna and external auditory canal collect the sound waves and funnel them to the ear drum, or *tympanum*. The ossicles and the air in the middle ear are caused to vibrate when the ear drum vibrates, and these vibrations activate receptors in the cochlea to give rise to the perception of sound. The ear drum is moved by vibrations of any audible frequency, but it does not resonate in response to any frequency. It is

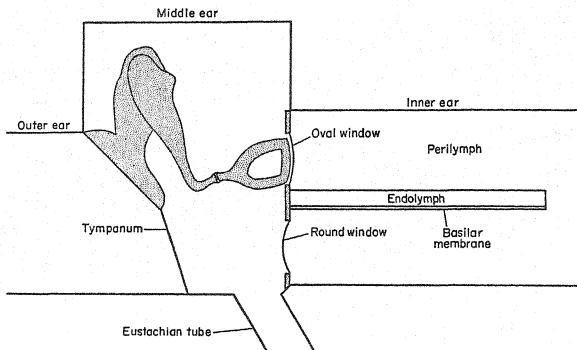


Figure 15-2. Schematic representation of the structures of the ear.

Usually the eustachian tube is closed. (From Youmans' *Basic Medical Physiology*.)

shaped like a blunt cone with the apex of the cone pointing inward. The *malleus* (hammer) is a little bone which is attached to the apex of the inner surface of the tympanum. Movements of the tympanum are transmitted to the malleus and then to the *incus* (anvil) and *stapes* (stirrup). The footplate of the latter ossicle is in contact with the oval window, and the leverages of the three ossicles working together are such that the footplate of the stapes moves through a distance about one-third as great as the movement of the center of the tympanum. The middle ear communicates with the pharynx by means of the *eustachian tube* through which air may enter or leave the middle ear and thus equal pressure can be maintained on the two sides of the ear drum. There are two minute

muscles, the *tensor tympani* and *stapedius*, which serve to keep the ear drum taut. These muscles contract reflexly in response to loud sounds to exert a damping action on the movement of the tympanum and thus protect the inner ear from damage from excessive vibrations.

The *cochlea* is a cavity in the temporal bone which derives its name from the fact that it is shaped like a snail's shell. The upper, smaller portion of the spiral tube is closed and the bottom contains two windows

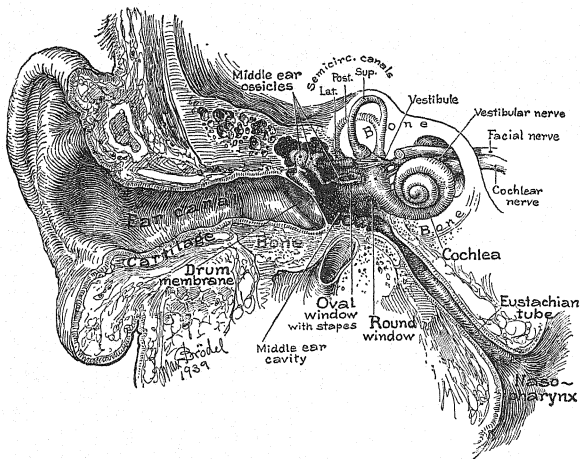


Figure 15-3. Anatomy of the ear.

This is a drawing by the famous medical illustrator Max Brödel. (Reproduced by permission of W. B. Saunders Co.)

sealed by a membrane. The upper of these openings is the *oval window* and the lower is the *round window*. The lumen of the cochlea is divided by membranes into three compartments: the *scala vestibuli*, *scala media*, and *scala tympani*. The *organ of Corti* which contains the endings of the auditory nerve and the receptors for hearing is located in the *scala media*, a closed tube filled with endolymph. The other two compartments, containing a fluid called perilymph, are connected at the apex of the cochlea.

When the foot of the stapes is displaced inward at the oval window, pressure is applied to the perilymph in the scala vestibuli. The pressure is transmitted to the scala media and this causes a downward movement of the basilar membrane which carries the organ of Corti. Also, the rise

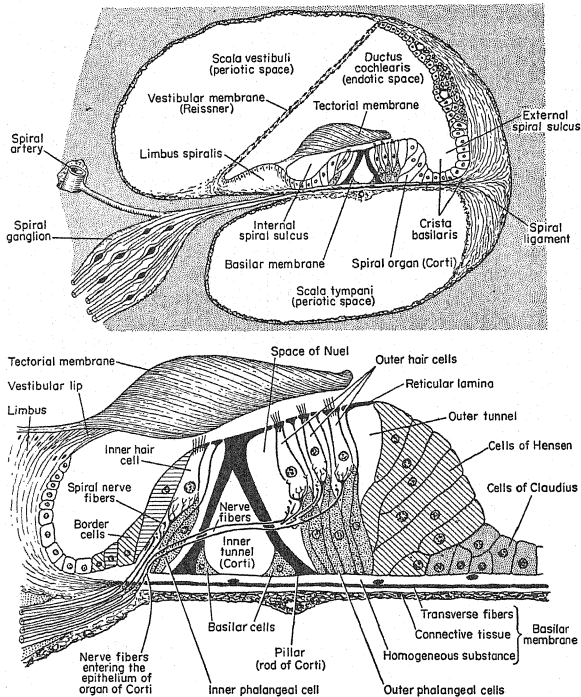


Figure 15-4. Microscopic anatomy of the cochlea.

Above: vertical section. Below: organ of Corti and basilar membrane shown on a larger scale. (By permission, after Rasmussen, *Outlines of Neuroanatomy*. Copyright, 1943, by Wm. C. Brown Co.)

Perception of Sound

Acuity of hearing is tested by means of an *audiometer*. This instrument produces frequencies of 64, 128, 256, 512, 1024, 2048, 4096 and 8192. A dial controlling intensity is set so that zero corresponds to the intensity at which that frequency is barely heard by an individual with normal hearing. If the intensity, expressed in decibels, must be increased above this level to be heard, there is hearing loss. If no sound is heard within the range of intensity from zero up to a level which is the threshold for feeling the vibration, hearing loss for that frequency is complete. Although, normally, sound waves are conducted to the inner ear mainly by the ossicular route, there is also conduction by the air in the middle ear, and under some conditions, the conduction is by the temporal bone. Frequently, there is loss of hearing for high frequencies only (*nerve deafness*) or low frequencies only (*middle ear or transmission deafness*). A third type of hearing loss, *central deafness*, is caused by lesions of the central nervous pathways or of the auditory cortex (page 166).

The human ear can discriminate very small differences in frequency, particularly within the range from 500 to 4000 cycles per second. Notes having a frequency differing by about 0.3 per cent can be detected as being of different pitch, and over the whole range of hearing there are approximately 1600 perceptible changes in pitch. The ear is not as efficient in detecting changes in loudness as it is for discriminating pitch. An increase in intensity of five to ten per cent is required under the best conditions, before there is a detectable difference in loudness, while at low frequencies and intensities a much greater per cent change is necessary in order to perceive a difference. The reduced ability to hear a given sound in the presence of another sound is known as *masking*. The masking effect is greatest for the frequencies just above and below that of the masking tone.

The ability to recognize the direction from which a sound is coming is well developed in some animals, but relatively poorly developed in man. Under the best conditions, it is difficult to locate the direction of the sound within ten degrees in the horizontal plane, and in the vertical plane errors are still greater. Localization of sound is possible because of the

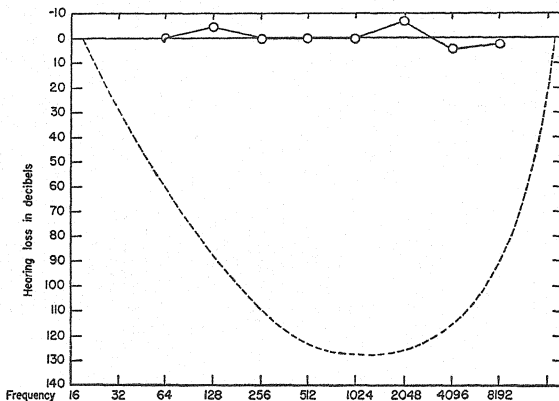


Figure 15-5. Chart for graphing results of audiometry.

Broken line indicates threshold for feeling, representing complete loss of hearing. When a reading at a given frequency lies below the zero line, the distance is measured, and the percentage of the total distance between the zero line and the broken line gives an expression for hearing loss at that frequency. Results of a test on a normal subject are designated by the circles. (From Youmans' *Basic Medical Physiology*.)

difference in the effects of the sound in the two ears. First, if the source of the sound is not equidistant from the two ears, there is a difference in the time of arrival; and second, if the source of sound is not directly in front of the subject, there is interference with the sound waves reaching the ear which is on the side farther away from the sound, hence the intensity is less.

It is a matter of common observation that the ear loses its sensitivity to sound when subjected to loud noises for a prolonged period. The reduction in sensitivity occurs in both ears following application of an intense

sound in one ear; therefore, it is possible that the loss of sensitivity is in part in the central connections rather than simply adaptation of the receptors in the ear. The loss of sensitivity is greater, however, in the stimulated ear.

Neural Pathways for Hearing

The organ of Corti is innervated by bipolar neurons of the spiral ganglion. The short peripheral processes pass from the cell bodies to the hair cells in the organ of Corti, and the long central processes enter the dorsolateral border of

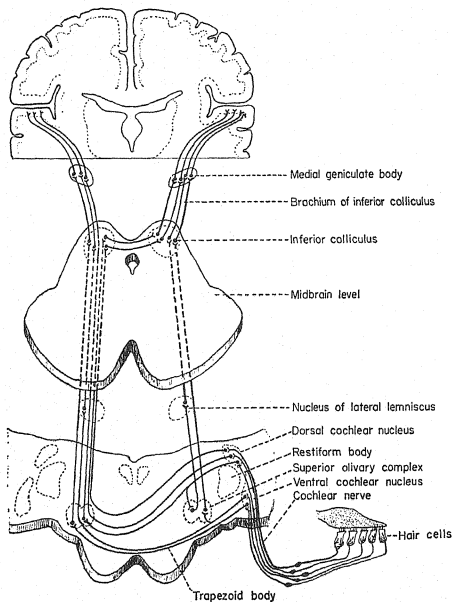


Figure 15-6. Diagram of neural pathways for hearing.

Note bilateral connections from the afferents from the hair cells on one side. (From Youmans' *Basic Medical Physiology*.)

the pons at its junction with the medulla and branch to make connections with the *dorsal and ventral cochlear nuclei* in the medulla on the same side. Some of the axons from cell bodies in these nuclei cross to the opposite side of the pons by varied paths and collect into a bundle, the *lateral lemniscus*, which

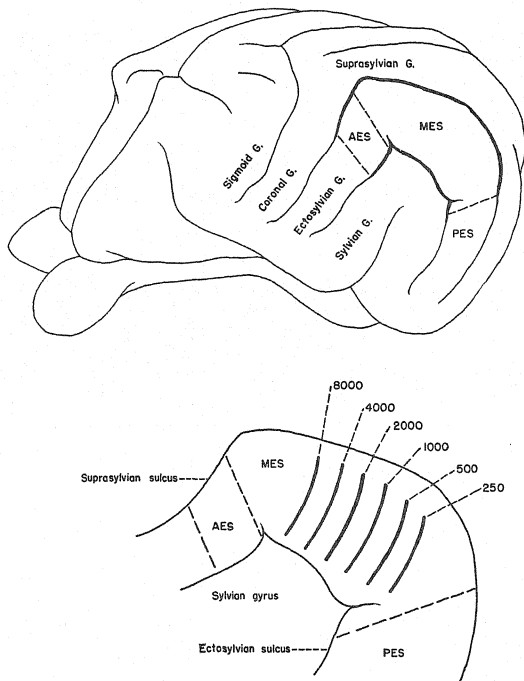


Figure 15-7. Representations of the cochlea in the cerebral cortex of the dog.

AES, MES, and PES indicate anterior, middle, and posterior areas respectively, of the ectosylvian gyrus. The numbers 250 to 8000 refer to frequency of vibrations in cycles per second used to stimulate the cochlea and evoke action potentials in the designated strips of cortex. (Reproduced by permission from A. R. Tunturi, *Am. J. Physiol.*, 162:493, 1950.)

passes up through the brain stem to form synapses with cells which give rise to axons passing to the *auditory area* of the cerebral cortex. This area is located on the inferior wall of the sylvian fissure in the temporal lobe (Figure 11-6, page 127). Also, a pathway for hearing is found in the lateral lemniscus of the same side, and this pathway is relayed to the auditory cortex of the same side. Experiments in which the cochlea and the auditory cortex of the same side were destroyed in one series of animals and the cochlea and auditory cortex of the opposite side were destroyed in another series, indicate that the uncrossed pathway for hearing is of about the same importance as the crossed pathway; hence destruction of the pathways on both sides is necessary to produce deafness.

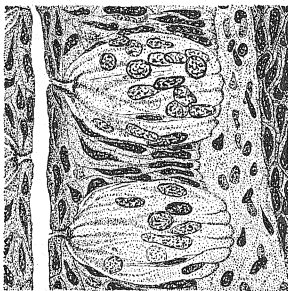


Figure 15-8. Taste buds on the sides of foliate papillae of the tongue of a rabbit.
Magnification about 540 times.

The localization of tones in the cochlea is preserved in the auditory cortex. It has been demonstrated that stimulation of a small group of fibers in the cochlea, electrically or by the use of sound of a single frequency, causes appearance of action potentials in a vertical strip of cortex in the temporal lobe. Stimulation at the base of the cochlea (high frequencies) evokes potentials in the most anterior strips of the auditory area of the cortex, while stimulation of the apex (low frequencies) elicits action in strips nearest the occipital region, and there is an orderly gradation of representation between these extremes.

Taste

The sense of taste is elicited when certain types of substances come in contact with the taste buds which are distributed chiefly over the

dorsal surface and edges of the tongue. The taste buds are minute ovoid structures which are composed of an external layer of supporting cells and a core of elongated cells ending in hair-like processes that project through a pore in the surface of the epithelium of the tongue. A row of circular (circumvallate) papillae is located in the shape of a V on the dorsal surface near the root of the tongue, and these papillae are richly supplied with taste buds. A few taste buds also are found in the epithelium of the epiglottis and soft palate.

It is generally considered that there are four fundamental or "pure" tastes: sweet, sour, salt, and bitter. The sensation elicited by tasting a food depends upon the combination of these, but smell also is a factor in the appreciation of the flavor of foods. Sourness is elicited by acids; saltiness is produced by chloride, bromide, iodide, nitrate, and sulfate ions; bitterness is elicited by a great number of substances classed chemically as alkaloids and by many of the cations; and sweetness is a property of sugars and many other chemically different types of compounds, such as saccharin and sugar of lead (lead acetate). The four kinds of taste are not similarly distributed, and one kind of taste may be depressed by means of drugs without causing a similar degree of loss of the other kinds of taste. From these and other facts, it is believed that, physiologically, there are four different types of taste buds corresponding to the four tastes.

Nerve fibers which innervate the receptors for taste pass from the taste buds by the chorda tympani and glossopharyngeal nerves and enter a pathway in the brain stem called the *tractus solitarius*. The secondary neurons in the taste pathway have their cell bodies in the nucleus of the tractus solitarius and give rise to fibers which pass to the thalamus of the opposite side. The tertiary neurons of the taste pathway project to the sensory area of the cerebral cortex.

Olfaction

The receptors for the sense of smell are located in the olfactory mucosa which occupies an area of about 2.5 sq. cm. in the upper portion of each nostril. The end organs for olfaction are rod-shaped structures which terminate in an expanded portion equipped with five or six hair-like processes. These cells are embedded in epithelial cells which are yellowish in color. The central end of the receptor continues as an unmyelinated nerve fiber through small openings in the bone to connect with the olfactory bulb of the brain. Thus, the receptor for the sense of smell is actually a differentiated neuron.

It is not possible to classify odors into a few definite components as can be done in the case of taste. Hence a number of terms must be used to describe odors. These include spicy, fruity, burnt, foul, resinous, etc. One of the striking features of the sense of smell is the rapid loss of sensitivity on exposure to a given odor. Within a few minutes one may no longer be aware of the odor, and recovery of sensitivity occurs equally rapidly following removal of the odorous substance. Masking of the odor

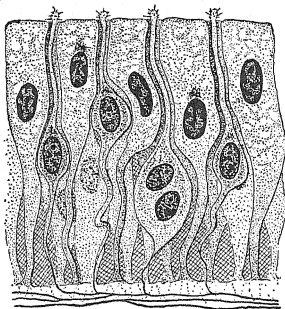


Figure 15-9. Portion of the olfactory mucous membrane.

Two major types of cells are seen: the olfactory cells and the supporting cells.

of one substance by the presence of another also occurs readily, and since the masking is produced, even when the two substances are applied to different nostrils, the phenomenon is, at least in part, central. The central pathways for olfaction are diffuse and quite complex. Most of the information concerning these pathways has been obtained from animals in which the sense of smell is more highly developed and more useful than in man. Deficiencies in the olfactory sense may be congenital or acquired. Complete lack of olfaction is known as *anosmia*.

Chapter 16

HIGHER FUNCTIONS OF THE CEREBRAL CORTEX

Association Areas

The technics of neurophysiology have been such as to permit localization of the principal receiving stations in the cerebral cortex and of the sites of origin of the efferent pathways which convey impulses to the motor neurons. After these primary sensory and motor areas have been delineated on the cortex, there remain relatively large so-called "silent," or *association*, areas. Three major regions are included: *orbitofrontal*, *anterior-temporal*, and *parieto-occipital* association areas.

A limited understanding of the function of the orbitofrontal association areas located at the anterior poles of the cerebral hemispheres has been derived by observing effects of destruction of this part of the brain. The symptomatology is quite diverse and there are marked variations from patient to patient; however, certain changes are encountered more frequently than others. Intelligence as tested by the less exacting methods is not conspicuously changed, but alterations of personality occur commonly. These consist of greater distractibility, lack of foresight, inappropriate emotional responses, and lack of appreciation of, or concern with, the consequences of one's behavior. Variations from individual to individual are great; one person may show negligible personality changes, while another hardly may be recognized as the same person.

It is possible and perhaps probable that, in the future, certain parts of the association areas will be found to be more important for some of the higher functions of the cerebral cortex than for others. In other words, some degree of localization of the higher functions may be demonstrated. However, the tendency at present is to consider that the higher processes of the brain require a certain minimal area of functional cortex and that

when enough cortex is destroyed to reduce the area below this minimum, evidences of impairment appear. This, if true, still gives no specific idea of how the brain accomplishes its higher functions.

In some diseases and in senility, changes occur which are attributable to impairment of the functions of the cerebral cortex. The subject reverts to earlier and simpler reaction patterns and emotional responses. The senile individual is said to be in his second childhood. Discriminative judgment is lost. The personality may change in various ways; there may be mild changes, such as excitability, bad temper, apathy, etc., or more severe alterations, such as antisocial acts which are carried out with little or no attempt to disguise them and without awareness of the unpleasant consequences of such behavior. Loss of memory of recent events is a particularly common and sensitive index of impairment of cortical function. However, failure to remember probably is due in some instances to lack of attention, and the two defects tend to be associated. It is apparent that memory is one of the most important functions of the brain, and the storage of information in the brain is perhaps the phenomenon which is most difficult to explain in terms of known functions of neurons.

Conditioned Responses

Functions of parts of the cortex, as well as other parts of the brain, have been studied by the use of conditioned reflexes or responses. Conditioned responses are established when a stimulus which normally does not evoke a response is associated repeatedly with another stimulus which elicits a reflex response. For example, if a dog is caused to salivate by any appropriate stimulus and the dog's skin is stroked at the same time, eventually, if the procedure is repeated often enough, the animal will be conditioned to salivate whenever the skin is stroked. A conditioned response is built up by repetition, and the process is more rapid if the conditioning stimulus is repeated frequently. Once a conditioned response is established, it persists for a fairly prolonged period. However, when it has been a long time since the animal has been exposed to the set of conditions which produced the conditioning, the response becomes weakened; but it can be rapidly built up again to the previous level.

Conditioned responses have been used experimentally to determine what an animal can differentiate by his senses and to learn what parts of the nervous system are concerned in the differentiation. For example, a

dog can distinguish between a circle and an ellipse as indicated by the fact that he can be conditioned to respond when he is shown one of these figures and not to respond when he is shown the other. Then, operations on the brain may be performed to determine what structures are essential to preserve the conditioned response.

Conditioned responses also can be used experimentally to produce "neuroses." Behavior reminiscent of neuroses in man can be produced in dogs, if, for example, the ellipse is made more like the circle so that the animal can no longer differentiate between the two figures. The animal displays anxiety and "temper tantrums" whenever faced with the experimental situation, whereas he performed quietly and efficiently when the difference between the two figures was such that he could easily distinguish them.

Agnosia, Apraxia, and Aphasia

The loss of memory of learned reactions may occur as a result of damage to certain areas of the cerebral cortex. The loss of ability to recognize common objects is known as *agnosia*. The sensory stimuli reach the brain, but the significance of such stimuli is not perceived. Tactile agnosia, or *astereognosis*, the failure to recognize objects by touch, already has been described. Psychic deafness, or *auditory agnosia*, was considered in the discussion of loss of hearing. *Visual agnosia* refers to inability of the subject to perceive the significance of objects seen. When the individual subject does not respond in an appropriate manner to tactile, visual, or auditory stimuli which he receives, before calling the deficit agnosia, it is necessary to establish that the failure to respond is due to lack of understanding rather than to inability to translate intentions into actions. In other words, the failure to respond may be due to paralysis rather than to agnosia. In some cases this differentiation may be difficult.

Whereas agnosia is a deficit "on the sensory side," failure to make appropriate responses may be due to impairment of ability to initiate the response, or *apraxia*. This is a defect "on the motor side," a defect in initiating "intended" actions. It is differentiated from paralysis in that the efferent pathway itself from the motor areas of the brain to the skeletal muscles is intact. The individual muscle groups may be activated by reflexes or as a part of simple automatic actions, but cannot be used in complex purposive acts.

Aphasia refers to disturbances of speech occurring on a basis other than paralysis of the muscles used in phonation. The inability to speak is one particular example of the inability to initiate appropriate voluntary movements, hence aphasia is one form of agnosia (receptive aphasia) or apraxia (expressive aphasia). There is a specific area located on the angular gyrus in the frontal lobes just above the sylvian fissure which seems to be most important for normal speech. Damage to this area on the left side in right-handed individuals commonly results in expressive aphasia.

The Electroencephalogram

The cerebral cortex shows rhythmic electric variations, the "brain waves," which have a low voltage and occur at several frequencies. In practice, the cortical potentials which are picked up by electrodes placed

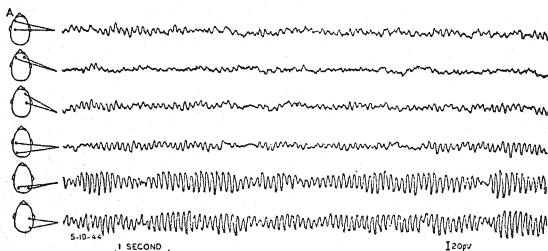


Figure 16-1. Normal electroencephalogram.

A record is obtained from each of six standard pairs of leads. (Reproduced by permission from Cohn, *Clinical Electroencephalography*. Copyright, 1949, McGraw-Hill Book Company, Inc.)

on the scalp are greatly amplified and fed into an ink-writing device. Usually the waves from several pairs of electrodes are recorded simultaneously. The record obtained is known as an *electroencephalogram*. Two types of waves are prominent: *alpha* waves occur at a rate of 8 to 12 per second, and *beta* waves are of a greater frequency and lower amplitude. The rapid waves are prominent in leads from the frontal and parietal regions, while the slow waves are dominant in the occipital region when the eyes are closed.

Clinical uses of electroencephalography are numerous, since the EEG pattern is altered by destructive or irritative lesions, by alteration in blood supply, etc. Characteristic patterns are associated with convulsive seizures, so that "abortive seizures" can be recognized, and sometimes similar abnormal patterns are seen between attacks in epileptics. In *petit mal* epilepsy, a condition characterized by momentary lapses of consciousness, a characteristic "spike-and-wave" pattern occurring at a rate of three per second is observed during the attacks and sometimes between attacks. The electroencephalogram is useful in the diagnosis and localization of brain tumors when they involve the cortex. In this case, the site of the abnormality is determined by means of several pairs of leads.

Chapter 17

BLOOD

The circulatory system is concerned mainly with transport. This is a problem which is encountered in any animal which is of any considerable size. The cells in the interior of the body are far removed from oxygen and nutrients in the environment, hence there is no possibility of direct interchange of nutrients and wastes between the cells and the surroundings. The respiratory and the circulatory systems function essentially as a unit in taking up and transporting oxygen to the cells and in removing carbon dioxide from them. Other wastes which result from catabolism must be carried from the cells to the kidneys. The hormones are transported from the various endocrine glands to the parts of the body where they exert their characteristic actions.

As already explained, the interchange of substances occurs between the blood plasma and interstitial fluid and in turn exchange occurs between the interstitial fluid and cell fluid. Normally, the volume and composition of the blood, except for the temporary changes associated with ingesting food and liquids, is maintained relatively constant. The concentrations of substances in the interstitial fluid likewise are maintained, since the capillary wall permits most of the constituents of the blood to pass readily by diffusion and filtration.

Fluid and Cellular Composition of Blood

Blood may be thought of as a tissue in which the intercellular substance is fluid. The fluid portion of the blood is known as *plasma*. When blood is withdrawn from a blood vessel and is placed in a container, a clot, derived from constituents of the plasma, is formed. The clot consists of shreds of protein, called fibrin, in which the cells are enmeshed. Just after the clot has formed, the fibrin strands cling to the wall of the con-

tainer and it can be inverted without spilling any portion of the blood; then, after a brief time, the clot begins to shrink away from the wall of the container and clear straw-colored *serum* appears surrounding the clot. Plasma differs from serum in that the plasma contains the protein which enters into the formation of fibrin, whereas serum does not contain this substance.

To prevent blood from clotting after it is withdrawn from a vessel, the blood may be introduced into a tube containing sodium oxalate or sodium citrate. When such blood is allowed to stand, the blood cells settle to the bottom of the tube and a layer of clear plasma appears. The separation of the cells from the plasma may be achieved rapidly by the use of a centrifuge. When blood is centrifuged until the volume of the red cells shows no further decrease, it is seen that about 45 per cent of a given volume of blood consists of cells and the remaining 55 per cent is plasma. The former reading is known as the *hematocrit*. It shows characteristic deviations from the normal range in disease. For example, it is low in anemia or just after a severe hemorrhage, and it is high in severely dehydrated persons.

The cells of the blood are of two main types, red blood corpuscles, or *erythrocytes*, and white blood corpuscles, or *leucocytes*. In addition, there are cell fragments known as blood platelets, or *thrombocytes*.

Erythrocytes and Hemoglobin

The erythrocytes are biconcave disks which are about 0.002 mm. (2 microns) thick and 0.008 mm. in diameter. The red cell contains no nucleus and the individual cells are a light greenish-yellow color when observed under the microscope. The pigment in the erythrocytes is hemoglobin.

The principal function of the red blood cell is to transport oxygen which is carried in combination with the hemoglobin. Hemoglobin is composed of a protein, globin, which is combined with the pigment, heme. The latter substance has the formula $C_{34}H_{32}O_4Fe$. Hemoglobin may exist in either the oxygenated or the unoxxygenated form, depending upon the availability of oxygen. Oxyhemoglobin is bright red in color, while the unoxxygenated, or reduced, hemoglobin is a dark purplish red.

Hemolysis. When a dilute suspension of red cells in 0.9 per cent NaCl solution is prepared, the suspension is semitransparent or foggy. If the red

cells are placed in hypotonic solutions, the hemoglobin is liberated from the framework of the cell, and this may be detected grossly by the fact that the solution becomes transparent. The following laboratory experiment serves to demonstrate how hypotonic a solution must be in order to cause hemolysis. To a series of each of six test tubes containing about 5 cc. of NaCl solution at concentrations of 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 per cent respectively, a drop of blood is added. In the tubes in which hemolysis occurs, the initial foggy appearance will change to bright transparent cherry red. This type of test affords a measure of *red cell fragility*. Hemolysis is produced also by certain fat solvents which dissolve constituents of the red cell framework. Ether and saponin are hemolytic; and the serious effects in man of some of the snake venoms are related to their hemolyzing action.

Production and destruction of erythrocytes. The number of red cells can be determined by diluting the blood with a suitable solution and counting under the microscope the number of cells in a given volume. Knowing how much the blood was diluted and the number of cells in a given volume of the dilute suspension, the number of cells per cubic millimeter of blood is obtained by a simple calculation. The normal range for adult males is about 4,500,000 to 6,000,000 and for adult women about 4,000,000 to 5,500,000. The erythrocyte count remains comparatively constant for a normal individual living in a given locality; if, however, this individual moves to a considerably higher altitude, one of the striking features of the slow acclimatization is the increase in the rate of production of red cells so that a new equilibrium between production and destruction is established at a higher count. Thus, the normal range for males living at 12,000 feet altitude is about 4,900,000 to 6,500,000 and at 15,000 feet it is 5,000,000 to 7,300,000. The hemoglobin content, which is expressed in grams per 100 ml. of blood, normally increases in direct proportion to the rise in erythrocyte count.

The red blood cells are produced in the red bone marrow, and it is known that a lowering of the oxygen tension in the circulating blood in some way causes the marrow to produce more red cells. Or, if erythrocytes are lost from the body by hemorrhage, there will be increased production of red cells until the previous level is restored. The precise mechanism by which such adjustments occur is not known.

The destruction of erythrocytes occurs in reticulo-endothelial cells mainly in the spleen and liver. These cells, which are found lining the smaller blood vessels, engulf and digest old or damaged red cells.

The production of the erythrocyte involves, first, the manufacture of the framework, or stroma, of the cell and second, the synthesis of the hemoglobin. For stroma production, a substance, known as the *hemopoietic* principle, is essential, and for production of hemoglobin, an adequate

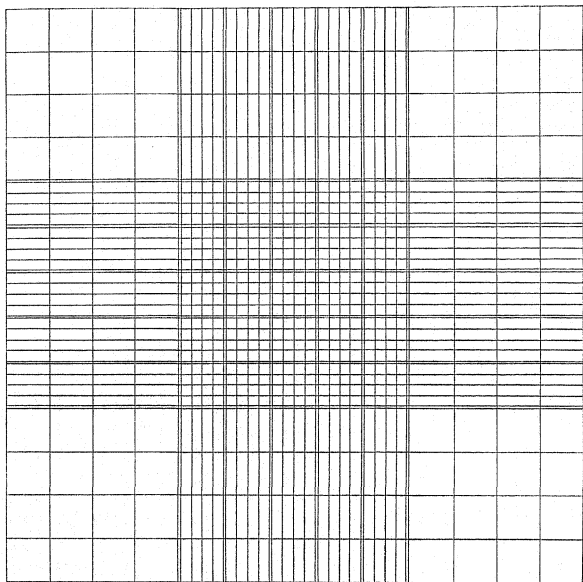


Figure 17-1. Ruling of erythrocyte counting chamber.

supply of iron is required. If there is a defect in either of these mechanisms, anemia results.

Anemia is the term which designates a deficiency in the amount of hemoglobin in the blood. It is not a disease, but is a change which occurs in many diseases. The number of red cells may be greatly reduced and may contain a normal, subnormal, or greater than normal amount of

hemoglobin per cell, or there may be a normal number of red cells with a subnormal amount of hemoglobin. There are two quite different groups of anemias: (1) those in which there is inadequate production of hemoglobin, and (2) those in which there is a deficiency in manufacture of the red cell stroma. A cause of the first type is the failure to include sufficient iron in the diet. This is an obvious cause, since iron is a component of hemoglobin. In most individuals on ordinary diets, the iron intake is adequate unless iron is being lost from the body more rapidly than normally.

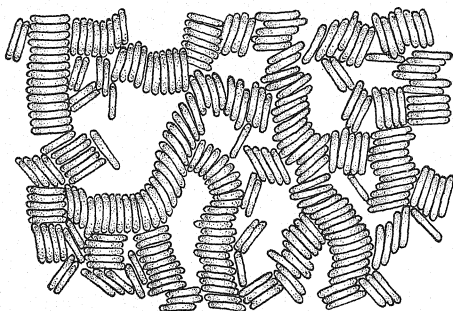


Figure 17-2. Erythrocytes in rouleaux.

A constituent of the diet (extrinsic factor) acting upon a constituent in the mucosa of the stomach (intrinsic factor) is converted into the hemopoietic material which is stored in the liver. In the disease, *pernicious anemia*, the body is permanently unable to produce the hemopoietic factor. Concentrated and purified liver extracts containing the hemopoietic factor have become available for injection for treatment of pernicious anemia, and red cell production may be kept at the normal level by one or two injections per month. This problem is considered further in the discussion of vitamin B₁₂ (page 368).

In the *iron-deficiency* anemias there is a mild or moderate decrease in red cell count, the cells are smaller than normal, and contain a less than normal amount of hemoglobin. The anemias resulting from a deficiency of the hemopoietic principle are characterized by a more severe reduction

in number of red cells, but the individual cells are large and contain normal amounts of hemoglobin.

Sedimentation rate of erythrocytes. Erythrocytes tend to adhere to each other to form *rouleaux*. The rate that the red blood cells will settle toward the bottom of a tube, leaving clear plasma above, is determined largely by the amount of such *rouleaux* formation, since the clumps of erythrocytes sink more rapidly than individual cells. *Rouleaux* formation, in turn, is accentuated by changes in the globulin fraction of the blood protein which occur in many infectious diseases. An increased sedimentation rate, therefore, is characteristic of many diseases.

Viscosity of blood. Blood is approximately five times as viscous as water. The viscosity of whole blood shows considerable changes and is determined largely by the red cell volume, being increased more or less in proportion to a rise in hematocrit and decreased in the presence of a lowered hematocrit. The viscosity of the plasma is low compared to whole blood and shows relatively minor changes. It varies with the concentration of the plasma proteins.

Leucocytes

The blood contains several types of cells which are not pigmented and hence are called white corpuscles or leucocytes. These cells are somewhat larger than the erythrocytes. They have irregular outlines and are nucleated. The types of white cells, their distinguishing characteristics, and relative numbers are indicated in the following classification:

A. Cells with granules in the cytoplasm and having a lobulated nucleus.

NORMAL %

- | | |
|--------------------------|---------|
| 1. Neutrophil leucocytes | 60-75 |
| 2. Eosinophil leucocytes | 3 |
| 3. Basophil leucocytes | up to 1 |

B. Cells without granules in the cytoplasm and having a large, non-lobulated nucleus.

- | | |
|----------------------------------|-------|
| 1. Lymphocytes (large and small) | 20-35 |
| 2. Monocytes | 4 |

The structural characteristics of these cells are illustrated in Figure 4-3. The white cell count for the blood of normal persons usually

ranges between 5000 and 10,000 per cubic millimeter, and approximately three-fourths of these cells are neutrophil leucocytes.

In disease, both the *total* number and the *relative* numbers of white cells change. The total number is determined by the same general methods used for counting red cells. The per cent of each type, or a *differential* count, is determined as follows. A drop of blood is smeared in a thin layer on a glass slide, and is dried and treated with a suitable stain. Usually, hematoxylin and eosin are used; the former is a basic stain, blue in color, and the latter is a red acidic stain. The basophil cells are so called because their cytoplasm takes the basic stain, the cytoplasm of the eosinophils takes the acid stain, and the neutrophils take both stains to some extent, so that a lilac color is produced. Also, as shown in the figure, the shapes of the nuclei and sizes of the granules of the cells are characteristic. Under high-power magnification, enough cells are counted and classified to establish the per cent of each type.

The cells of the granular series are produced in the red bone marrow, intermingled with the cells from which the erythrocytes arise, and it is possible that the granular leucocytes and red cells have a common precursor. The lymphocytes are produced largely in the lymph nodes and spleen. Lymphatic elements also are found in the adenoids, tonsils, and in the wall of the small intestine.

Functions. The neutrophil cells, also known as polymorphonuclear leucocytes or "polymorphs," are produced in large numbers in some of the diseases which are caused by bacteria. The white cell count may go up to 30,000 or more and 98 per cent of the cells may be neutrophils. The rise in white cell count is called *leucocytosis*. In a local invasion of the body by bacteria, as in an infected wound of the skin, the injured area becomes thickly packed with neutrophil leucocytes, which wall off the infection and ingest the bacteria, and some of the white cells are destroyed and disintegrate. Pus is composed in considerable part of liquefied white corpuscles. The specific role of the neutrophils in combating many acute infections is indicated by the fact that only this type of cell shows an increase in the number in the blood. However, there are some infections, usually of a more chronic type, in which the rate of the production of lymphocytes is increased, and in some of these conditions the lesion produced by the infecting organism is infiltrated by lymphocytes.

It is apparent that bacteria which invade the body either liberate or cause the local production of substances which are carried to the bone marrow or lymph tissues where they stimulate the production of leuco-

cytes or lymphocytes. Evidence is accumulating that the lymphocytes are concerned with the production of substances called antibodies (page 464) which are a part of the body's defense against diseases caused by micro-organisms.

The monocyte acts as a scavenger in that it ingests and digests small fragments of cells. The functions of the eosinophil and basophil cells are not well understood; however, the former increase in numbers in allergic diseases, such as asthma, and in parasitic infestations.

The role of the white blood cells in the body's defense against bacterial invasion becomes obvious in conditions in which the white cell count decreases to below 500 per cubic millimeter, in which case even minor infections commonly cannot be combatted. There is a group of diseases, known as the *leukemias*, in which white blood corpuscles enter the blood in very large numbers, and various types of immature forms are present in the circulating blood. The predominant type of white cell may be either mature or immature cells in either the lymphocytic or leucocytic series.

Thrombocytes. In addition to the erythrocytes and leucocytes, the blood contains fragments which are known as platelets or *thrombocytes*. The normal number is between 200,000 and 400,000 per cubic millimeter. The thrombocytes are thought to be derived from giant cells of the bone marrow, or *megakaryocytes*, which are about 40 microns in diameter and exhibit ameboid movement. Thrombocytes break down to furnish factors which catalyze the clotting of blood. A deficiency in the number of thrombocytes is associated with an increase in the time required for blood clotting.

Composition of Blood Plasma

The blood plasma consists of about 90 to 92 per cent water and 8 to 10 per cent solids. Of the latter, only about 10 per cent is inorganic (sodium, calcium, potassium, magnesium, phosphorus, etc.). The proteins of the blood plasma make up 70 per cent of the solids and the remaining 10 to 20 per cent contain a number of non-protein nitrogenous substances (urea, uric acid, purines, amino acids, creatine, creatinine, etc.), lipids, cholesterol, and glucose. The blood plasma contains the respiratory gases, oxygen and carbon dioxide, in solution and in combination with other substances. Finally, the blood plasma is the medium for carrying all of the

hormones and various enzymes and antibodies which are present only in traces.

Plasma proteins. The proteins of the blood plasma are important in the blood clotting mechanism, in the maintenance of the osmotic tension of the blood above the level of the interstitial fluid, and as a source of protein for the tissues. The osmotic effect of the plasma protein, drawing fluid into the capillary, is essential for keeping the blood volume up to, and the interstitial fluid down to, normal levels (page 30). Fibrinogen is the principal protein which, on coagulation of the blood, is converted to

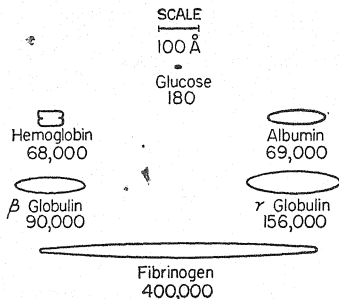


Figure 17-3. Molecules of blood protein drawn to the same scale.

Numbers indicate molecular weights. (Reproduced by permission from Oncley, *Symposia on Nutrition*, Vol. II, "Plasma Protein." Copyright, 1950, by Charles C Thomas.)

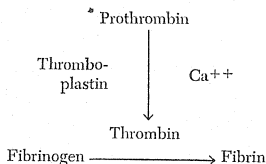
fibrin. The fibrin may be removed from the blood simply by whipping or stirring the freshly drawn blood with a bundle of fine wires. Fibrinogen has a molecular weight of about 400,000. The protein which is present after defibrination is divided into serum *albumen* and serum *globulin*. The globulins are proteins having a molecular weight around 90,000 to 160,000 which are precipitated by half saturation with ammonium sulfate. They include alpha, beta, and gamma fractions, with the latter having the higher molecular weight (Figure 17-3). The remaining albumen is of lower molecular weight (69,000) and is precipitated by full saturation with ammonium sulfate. Thus, the initial division of the protein into two portions is arbitrary. Normal human plasma contains 3.7 to

4.7 per cent of albumen and 1.9 to 3.6 per cent of globulin (including 0.4 per cent of fibrinogen), and the albumen-globulin ratio is normally roughly 2:1. In some conditions, for example, in renal disease where the protein which escapes into the urine is mainly albumen, the albumen content of the blood is greatly decreased and may be lower than the globulin.

Coagulation of the Blood

The clotting of blood is a process which is familiar to everyone. The obvious purpose of clotting is the formation of a plug or seal to prevent further loss of blood from the broken wall of a vessel. The serious consequences of failure of the blood to clot are seen in diseases such as hemophilia, but just as important to the survival of the organism is the maintenance of the fluidity of blood while it is within the intact vessels. Hence a discussion of clotting must include consideration of why blood does not coagulate in the circulatory system, yet does clot when it escapes from the vessels. Also, it is necessary to understand how certain substances prevent coagulation.

Generally, coagulation is described as occurring in two major steps. (1) A pro-enzyme in the blood, *prothrombin*, is acted upon by a substance, *thromboplastin*, in the presence of calcium ions to produce the active enzyme, *thrombin*. (2) *Thrombin* acts upon the soluble plasma protein, fibrinogen, to produce the insoluble *fibrin* which is the essential part of the clot. The steps are diagrammed as follows:



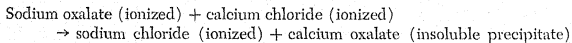
Thromboplastin, or thrombokinase, is found in all tissues, and the lungs and brain are especially rich sources. Also, disintegrating thrombocytes are thought to liberate small amounts of thromboplastin and this explains, in part, the fact that blood will clot, after some delay, even when it is withdrawn from the blood vessel in such a way as not to come in contact

with any tissue fluid. The blood remains fluid in the vessels, evidently because thromboplastin does not accumulate in adequate amounts and because an antithrombin is present in normal blood. If thromboplastin is injected intravenously, intravascular clotting will occur. When blood is shed from a vessel, the tissue supplies the thromboplastin and the thrombocytes disintegrate to provide a factor, known as *platelet accelerator*, which increases the rate of the clotting process. It is believed that the globulin fraction of the blood also contains one or more factors (*accelerator globulin*) which are concerned with accelerating the coagulation of blood.

Under abnormal conditions, a clot, or *thrombus*, may form within a blood vessel. Prolonged stasis in a vein is one of the more obvious causes of *thrombosis*. When this occurs, the clot either becomes fixed to the vessel wall by reparative processes resembling scar formation and subsequently becomes recanalized, or the thrombus breaks loose and is carried on to another portion of the cardiovascular system where it may produce symptoms depending upon the organ involved. A dislodged thrombus is known as an *embolus*.

Heparin, found in the liver and, apparently, also in the lining of blood vessels, interferes with the action of prothrombin and thrombin. It may be a factor in the maintenance of the fluidity of the blood within the vessels. If a segment of vein is occluded gently, so that the lining of the vessel is not damaged, the blood may remain fluid for a prolonged period. Hence, although stasis is a contributing factor, clotting within a vessel may not occur, unless other abnormalities also are involved.

Since the activation of prothrombin depends upon the presence of calcium ions, the addition of sodium oxalate which precipitates the calcium prevents clotting.



Also, the ionized calcium may be removed and clotting prevented by the addition of sodium fluoride or sodium citrate. Sodium citrate and sodium oxalate commonly are used to prevent the clotting of blood which has been withdrawn for chemical analysis or for transfusion.

Hemophilia is a disease which is transmitted to male children through females who themselves do not have the disease (see page 447). The disease is characterized by severe hemorrhage from minor injuries. Since blood from hemophiliacs clots normally if thromboplastin is added, it

evidently contains prothrombin and fibrinogen. Also, the blood of hemophiliacs contains platelets in adequate numbers.

Another group of diseases is distinguished by a deficiency in the number of blood platelets. Evidently, capillary walls frequently are ruptured and are quickly repaired with fibrin. When the repair does not occur, there is oozing through the breaks, and hemorrhagic spots are seen in the skin or mucous membranes. When these become numerous, a typical rash, or *purpura*, is produced. Purpuras may develop from deficiency in the number of platelets or from abnormal fragility of the capillary wall or from deficient clotting due to lack of prothrombin secondary to vitamin K deficiency (page 363). More rarely, hemorrhagic states may result from failure of the liver to manufacture prothrombin or fibrinogen when this organ is severely damaged.

Antigen-Antibody Reactions and Blood Groups

The proteins which are normally present in the blood are built up in the body from amino acids derived from digestive processes. Some of the proteins found in each species are characteristic for that species, and proteins from other sources are referred to as "foreign" protein. If a foreign protein is taken into the digestive tract, ordinarily it is digested into the amino acids which may be reconstituted into the protein of the type found in the body. Hence none of the original molecules of the foreign protein get into the blood. When foreign proteins are injected into animals, the tissues of the animal are stimulated to produce substances known as *antibodies*. The foreign protein itself is called an *antigen*, and the chemical reactions which occur in organisms as a result of injection of foreign protein are known as antigen-antibody reactions. Such reactions form an important part of the processes by means of which the human body protects itself against diseases caused by microorganisms. The antigen may be a toxic substance liberated by bacteria in the body, and the antibody which is produced may be capable of neutralizing the action of the toxic material. When the body has been subjected to a toxin and has produced antibodies to neutralize the toxin, the person is said to have immunity with regard to that particular substance. The relative amount of antibody present in the blood, or *antibody titre*, increases as one is repeatedly subjected to the antigen, and the titre gradually decreases during a period when none of the antigen enters the blood.

Some antigen-antibody reactions are harmful to the organism. The anaphylactic reaction, or *anaphylaxis*, will serve to illustrate this. A guinea pig is given a considerable dose of a foreign protein, and no reaction whatever to this initial injection is observed. Then, when a second dose is given two or three weeks later, constriction of the smooth muscle in the walls of the terminal air passages in the lungs develops so that the guinea pig may suffocate unless a drug is injected which will cause relaxation of the smooth muscle. The second dose of foreign protein, known as the *shocking dose*, may be quite small as compared with the initial or *sensitizing dose*. From this fact, it is apparent that a striking chemical change has been induced in the animal following the first dose. This chemical

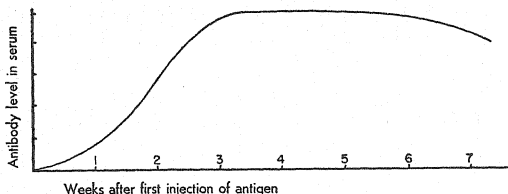


Figure 17-4. Diagram of level of antibody in serum following injection of antigen.

(From Youmans' *Basic Medical Physiology*.)

change is not of itself harmful and, in fact, is not evident until another dose of the foreign protein is injected. It is considered that in the experiment just described, an antibody is produced in the smooth muscle cells following the first injection and later when antigen is injected and unites with this antibody, the substance which is produced causes contraction of the cells. Some of the evidence for this view is based on studies which show that there is persistence of sensitivity of smooth muscle cells to the antigen, even after the smooth muscle has been removed from the body.

Blood groups. The well-known blood groups are established on the basis of antigen-antibody reactions. There are two proteins designated by A and B which may be present in the red blood cells. In any one individual, either or both of these proteins may be present; however, in some persons, neither A nor B is present. This is the basis for the four blood groups: A, B, AB, and O. The proteins A and B are foreign proteins for

those persons who do not have them in their red cells; furthermore, an individual has antibodies in his blood plasma against whichever of these proteins is not present. Thus, a subject who has blood of group A has protein A in his red cells, and he has anti-B in his blood plasma, but does not have anti-A. A person having blood of group B has protein B in his red cells and anti-A in his plasma, but no anti-B. Individuals having blood of group AB have protein A and B in their red cells and have neither anti-A nor anti-B in their plasma; while persons with blood group O have neither protein A nor B in their red cells, but have anti-A and anti-B in their plasma. The information about blood groups is essential for determining whether blood from one person may be transfused into another. If red cells having one of the proteins, for example A, are introduced into the blood of another person who has anti-A in his plasma, the red cells will clump together, or agglutinate, in the recipient's plasma. The recipient will have anti-A in his plasma, if his blood is of group B or O. The agglutinated red cells cause ill effects because they occlude small vessels and also because they hemolyze and disintegrate. Typical symptoms which constitute what is called a "transfusion reaction" occur following the injection of incompatible blood. The following table shows which types of blood are compatible, that is, do not cause transfusion reactions, and which types are incompatible.

BLOOD GROUP OF RECIPIENT		BLOOD GROUP OF DONOR (i.e., agglutinogens in cells)			
Group (i.e., agglutinogens in cells)	Agglutinins in serum of recipient	A	B	AB	O
A	Anti-B	—	+	+	—
B	Anti-A	+	—	+	—
AB	None	—	—	—	—
O	Anti-A and Anti-B	+	+	+	—

The minus sign indicates that agglutination does not occur and the plus sign signifies agglutination. The proteins in the cells are called agglutinogens and the antibodies in the plasma are called agglutinins. It will be noted that individuals having blood of group AB, since they have neither anti-A nor anti-B in their plasma, can receive blood of any group, hence they are called *universal recipients*. Also, note that blood of group O can

be given to any group. Persons having this type of blood are called *universal donors*.

In transfusing blood, in general, one does not need to be concerned with effect of the donor's plasma on the red cells of the recipient because the plasma is being introduced slowly and any anti-A or anti-B present in the donor's plasma is diluted by the plasma of the recipient to concentrations which are not sufficient to produce agglutination of the recipient's

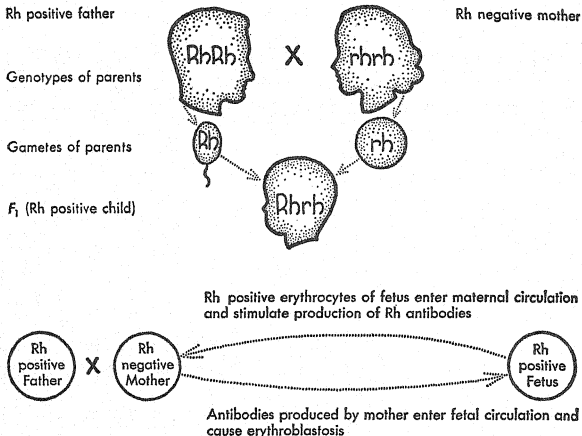


Figure 17-5. *Above*, inheritance of Rh incompatibility. *Below*, diagram of mechanism of production of erythroblastosis.

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red cells. Nevertheless, it has been found to be better to give blood of the same group, whenever this is possible. Furthermore, even when the blood of the donor is of the same group as that of the recipient, it is important to mix the two bloods on a glass slide and examine under the microscope to see if agglutination occurs. This procedure is known as *cross-matching*.

The Rh factor. In addition to the A and B antigens, there are several other substances in blood which make necessary additional precautions

when blood is transfused. The erythrocytes of about 85 per cent of the white population contain a substance called the Rh antigen. Normally, no antibody is present in the serum to react with the Rh antigen, and this is true both in persons having the antigen (Rh positive) in their red cells and in those not having the antigen (Rh negative). The difficulties arise from the fact that an Rh negative patient will develop antibodies in his plasma in response to a transfusion with Rh positive blood; hence if he is transfused a second time with Rh positive blood a transfusion reaction may be expected to occur.

The discovery of the Rh factor has led to an understanding of a condition in the newborn child known as *erythroblastosis fetalis*. This relatively uncommon disease has been known for a long time. It has been observed that *erythroblastosis fetalis* may appear in children of an Rh positive father and an Rh negative mother. Since the Rh antigen is inherited as a dominant characteristic, the infant will be Rh positive also. Now, although the blood of the mother and the fetus do not mix, they do come in close contact in the placenta, and in some cases the blood of the Rh negative mother develops antibodies against the Rh antigen in the blood of the fetus. The anti-Rh in the mother's blood then diffuses into the blood of the fetus and causes massive destruction of the red cells of the fetus. Ordinarily, the development of anti-Rh does not occur in the mother's blood during the first pregnancy, but once the condition makes its appearance in an infant it can be expected that all subsequent infants born to those parents will be affected.

Chapter 18

GENERAL FEATURES OF THE CIRCULATORY SYSTEM

Structural Organization

The vertebrate heart, depending on the class, consists of one or two chambers, known as auricles or atria, which receive blood returning to the heart by the veins, and the atria empty into chambers, known as ventricles, which pump blood into the arteries.

The circulatory system of mammals is diagrammed in Figure 18-1. Blood is pumped from the right ventricle through the pulmonary arteries to the lungs, and returns by the pulmonary veins to the left auricle; then, it passes to the left ventricle which pumps it into the aorta and thence by the systemic arterial tree to capillary beds throughout the body. Blood returns by the systemic veins to the right auricle. The circuit to the lungs is called the *pulmonary* or lesser circuit, and the circuit which receives the blood from the left ventricle is called the *systemic* circuit. It should be noted that the distinction between veins and arteries is made on the basis of direction of flow of blood with reference to the heart (arteries carrying blood away from the heart and veins carrying blood returning to the heart) and not on the basis of oxygen content of the blood. Oxygenated blood is found in the veins of the pulmonary circuit and the arteries of the systemic circuit, and blood which is low in oxygen content is found in the systemic veins and in the pulmonary arteries.

Since normally there is no flow of blood from the left side of the heart to the right side, the circulation may be diagrammed, as in Figure 18-2, to emphasize certain physiological principles. In this diagram, it is shown that, although anatomically there are two circuits, when the route of a blood cell is considered, there is one circuit containing two separate

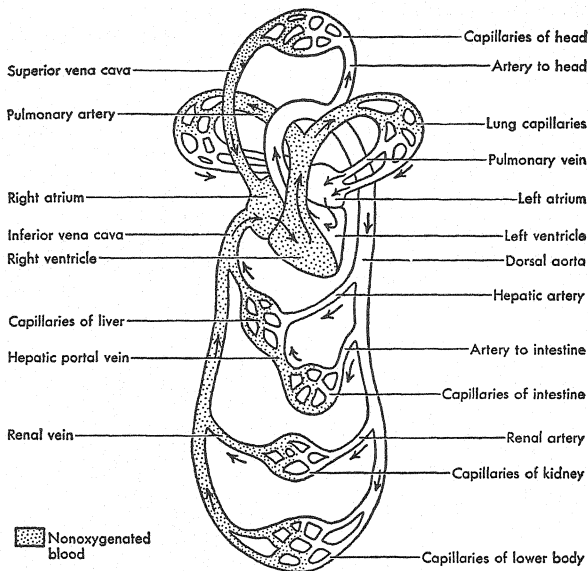


Figure 18-1. Diagram of the principal features of the circulatory system.

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pumps which sometimes are referred to as the "right heart" and "left heart." From Figure 18-2, it is apparent that the amount of blood flowing per unit of time through any cross section of the system cannot be different from the flow at any other cross section for very long; otherwise blood would accumulate progressively at some site in the system. Thus, during any prolonged period, the output of the right ventricle must equal that of the left ventricle.

Although the right and left ventricles pump the same amount of blood, the mean pressure in the aorta is about six times as great as the mean pressure in the pulmonary artery. Therefore, the work done by the left

ventricle is approximately six times as great as the work done by the right ventricle. The musculature of the left ventricle is about three times as thick as that of the right ventricle.

The auricles have thin muscular walls and are relatively distensible. They contract to assist in the transfer of blood into the ventricle; but, since the pressure in the ventricles is near zero at the time of auricular contraction, these chambers do relatively little work. In lower vertebrates,

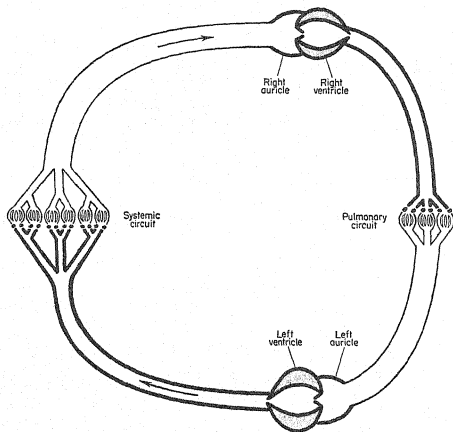


Figure 18-2. Diagram of circulation to aid in visualizing facts concerning volume of blood flow and pressure in the systemic and pulmonary circuits.

the auricular contraction may be important for producing ventricular filling; but in mammals, ventricular filling is easily accomplished because of the higher pressure in the great veins than in the ventricle when the ventricular muscle is relaxed, even in the absence of any pumping action of the auricles.

The walls of the arteries are thick, elastic, and distensible. The veins have thinner walls than the arteries and are more distensible. Therefore, the arteries will undergo considerable changes in pressure with minor changes in volume; on the other hand, the veins show a considerable change in volume with minor changes in pressure.

Most of the blood vessels contain smooth muscle in their walls, but the smooth muscle coat is most prominent in the arterioles. The tonus of the smooth muscle in the arterioles is controlled by neural and humoral mechanisms. This permits them to function as "stopcocks," and affords a basis for regulating the flow of blood from the arterial tree into the various capillary beds.

The capillaries are very thin walled. As they are quite distensible, they undergo considerable changes in volume in the presence of slight changes in pressure. The main functions of the cardiovascular system are per-

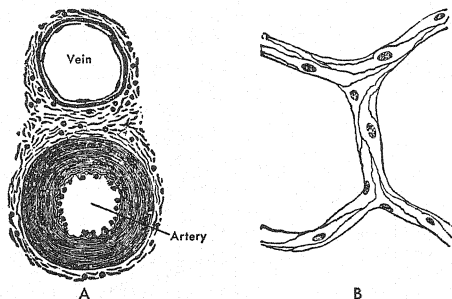


Figure 18-3. Structure of blood vessels.

A, Cross section of a small artery and a small vein. B, Capillaries from the mesentery. The capillary wall consists of one layer of cells. The dark ovoid bodies are nuclei. (Reproduced by permission from Kimber, Gray, Stackpole and Leavell, *Textbook of Anatomy and Physiology*. Copyright, 1961, by The Macmillan Company.)

formed in the capillary beds where an interchange of materials, through the capillary wall, between blood plasma and interstitial fluid occurs. This serves to maintain a constant composition of the interstitial fluid, which constitutes the environment of the body cells.

The distribution of the principal arteries of the systemic circuit is illustrated in Figures 18-4 and 18-5. The first portion of the aorta is known as the ascending aorta. It gives rise to the two coronary arteries which supply the heart. The next portion, the arch of the aorta, gives rise to the innominate (nameless) artery which divides into the right subclavian and right common carotid arteries. The next branch which comes off from the transverse aorta after the innominate is the left

common carotid artery, and next is the left subclavian artery. The main arteries to the head on each side are the common carotid and the vertebral. The latter is the first branch from the subclavian artery. It passes up along the vertebral column and enters the cranium through the foramen magnum. At the lower border of the pons, the two vertebral

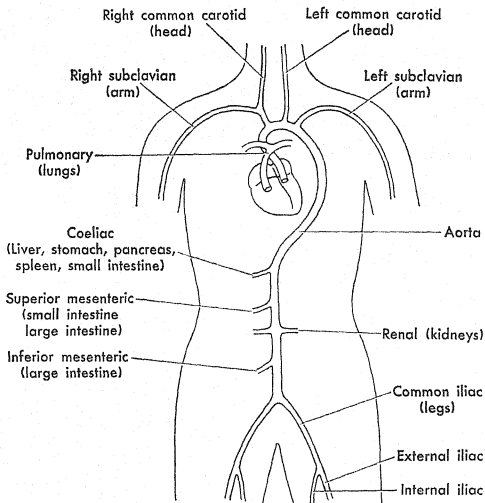


Figure 18-4. Main arteries of the trunk and limbs.

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arteries unite in the midline to form the basilar artery. The common carotid is the main artery of the neck and head. It divides into the external and internal carotid arteries. The physiologically important *carotid sinus* is found as a slight dilation at the initial portion of the internal carotid artery, and the *carotid body* which, like the carotid sinus, contains sense organs important in the control of circulation and respiration is found in the crotch formed by the bifurcation of the common carotid artery.

The subclavian artery on each side continues as the axillary, and in the upper arm as the brachial which divides at the level of the elbow into radial and ulnar branches. Blood pressure usually is recorded from the brachial artery. The pulse at the wrist level can be palpated in either the radial or the ulnar arteries. The arch-like arrangement of the vessels

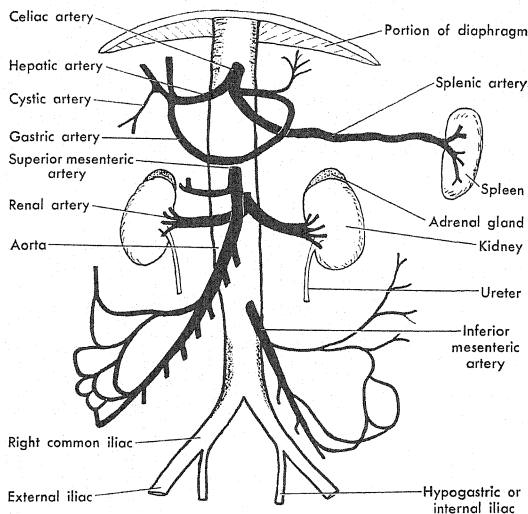


Figure 18-5. Main arteries of abdominal cavity.

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in the hand is such that extreme reduction in blood flow to the hand occurs only if both radial and ulnar arteries are occluded. If one of these vessels alone is occluded, blood supply can be maintained through the other.

The thoracic aorta gives rise to paired intercostal arteries which accompany each pair of ribs. The abdominal aorta gives rise to the following

large vessels (from above downward): the celiac axis which supplies most of the organs in the upper abdominal cavity, the superior mesenteric artery, a pair of renal arteries, and the inferior mesenteric artery. The abdominal aorta terminates in the two large branches, the right and left common iliac arteries. Each of these gives rise to a hypogastric branch and continues as the external iliac. The latter gives rise to the deep femoral

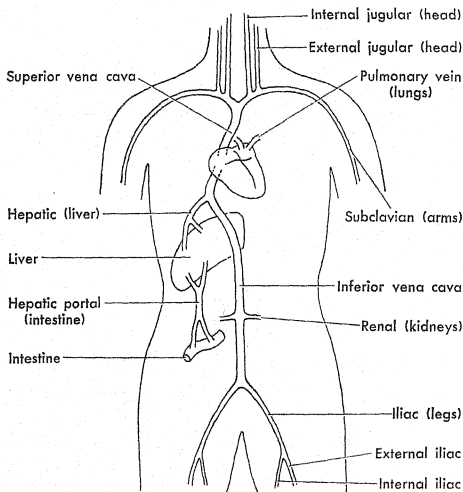


Figure 18-6. Main veins of the trunk and limbs.

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artery and continues as the femoral artery. The femoral continues as the popliteal at the level of the knee and divides into anterior and posterior tibial branches.

A diagram of the systemic venous system is shown in Figure 18-6. It may be noted that the general arrangement of the venous system is somewhat similar to that of the arterial system. The two principal veins drain-

ing blood from the head are the external and internal jugular. The latter is in close proximity to the carotid artery. Two large veins connect with the right atrium. The one entering from above and draining blood from the upper extremities and head is the superior vena cava. The one enter-

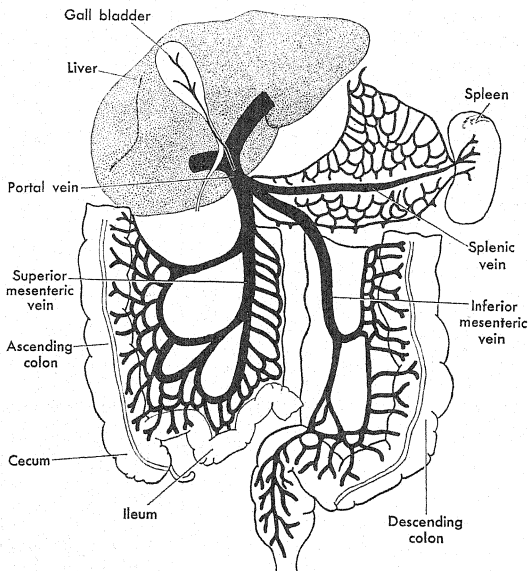


Figure 18-7. Portal venous system.

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ing from below, carrying blood returning from the trunk and lower limbs, is the inferior vena cava. The portal system of veins (Figure 18-7) is unusual in that blood which passes from capillary beds in abdominal organs enters another capillary bed in the liver. The significance of this arrangement is considered in Chapter 28.

Elementary Hemodynamics

Hydrodynamics is a term which refers to the study of physical laws governing flow of water, and the term *hemodynamics* designates the study of the laws governing the flow of blood. Flow of any liquid is related to the pressure exerted by the liquid against resistance. For example, the rate of flow of water from a faucet is determined by the pressure in the pipe and the extent to which the faucet is opened. The latter is the resistance factor and it is greater, the more nearly the faucet is closed.

In the case of the circulation, there is transfer of a given amount of blood per unit of time into an elastic system of branching tubes (the arterial tree) which become progressively larger in total cross sectional area and progressively smaller in caliber as the arterioles and capillaries are approached. The blood meets relatively little resistance in the larger vessels, but encounters considerable resistance in the arterioles. Hence the large vessels are analogous to the water pipe and the arterioles serve as numerous small faucets. The analogy is applicable further in that the arterioles have a relatively thick coat of smooth muscle which may contract or relax and hence change the caliber of the lumen.

There is pressure in the arterial tree for the same reason, for example, that there is pressure in a balloon that has been inflated with air; namely, there is sufficient volume of contents to fill and distend an elastic system. In the case of the arterial tree, the blood is escaping through the arterioles, but it is being continually replaced as a result of the pumping action of the heart.

Pressure exerted against the wall of a blood vessel can be expressed in terms of the height of a column of liquid that can be supported by the pressure. The pressure exerted at the base of the column of liquid is referred to as *hydrostatic* pressure. Before considering pressures and pulsations in the heart and arteries, it is instructive to learn certain simple factors which determine the rate and volume of flow of liquid through small tubes. The classic setup for illustrating these factors is shown in Figure 18-8. There is a reservoir which connects with a horizontally placed tube and at intervals along the horizontal tube, upright tubes are placed to obtain a measure of lateral pressure. If, now, the reservoir is kept filled to a certain level, flow out of the system at the end of the horizontal tube will occur at a steady rate and each of the perpendicular tubes will show a different pressure level. It is apparent that occlusion of the outlet

through which the liquid is flowing would cause the height of the water in the vertical tubes to rise and equal that in the reservoir, since water seeks a level. In this initial experiment, it is illustrated that the head of pressure is used up in overcoming the resistance to flow which is imposed by the small tube of the length shown. The greater the hydrostatic pressure, other factors being equal, the greater will be the amount of liquid that will flow through the lateral tube per minute. On the other hand, if the length of the horizontal tube is increased, the volume of flow will be

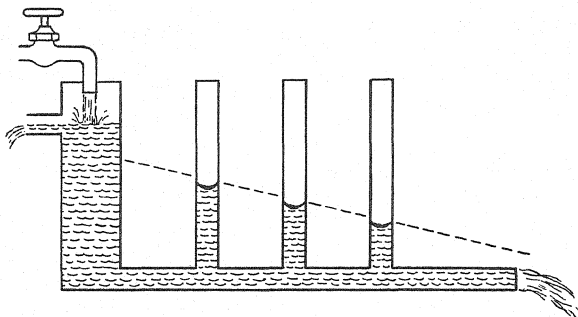


Figure 18-8. Diagram to illustrate that a given constant head of hydrostatic pressure produces a certain constant amount of flow through a small tube and that the lateral pressure falls progressively along the tube.

correspondingly decreased, if the head of pressure is kept constant; or, in other words, if flow is to be maintained through a longer tube, which offers proportionately greater resistance, a corresponding increase in the head of hydrostatic pressure will be needed.

The next model (Figure 18-9) serves to illustrate effects of changes in resistance to flow in a small tube. In this case, the horizontal tube is equipped with a stopcock which may be opened or closed. In the upper part of the diagram, the conditions seen when the stopcock is wide open are illustrated. When the stopcock is partially closed, as shown in the lower diagram, the level in vertical tube A increases, while that in tube B decreases. At the same time, the total amount of fluid which escapes per minute decreases. Complete closure of the stopcock would of course

cause A to rise to equal the level in the reservoir, while the level in B would decrease to zero, and outflow from the system would cease.

The human heart pumps intermittently by means of a sudden contraction of the entire ventricular musculature, then it relaxes and remains

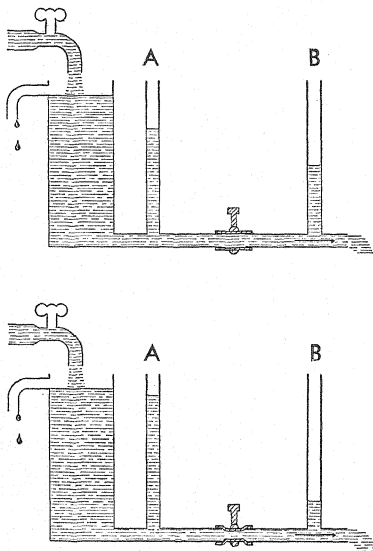


Figure 18-9. Diagram to illustrate that a local reduction in caliber in a small tube causes a rise in lateral pressure upstream (A) and a decrease in lateral pressure downstream (B) when the head of pressure producing the flow is kept constant.

Outflow per minute is decreased when the caliber of the tube is reduced, since resistance to flow is increased without a corresponding increase in the head of pressure.

quiescent for a brief period until the next contraction. Hence the cardiac cycle is divided into two main parts, the contraction phase being called systole (*sis'to-le*) and the resting phase of the cycle, diastole (*di-as'to-le*). The duration of these periods is unequal, the diastolic period, at normal

heart rates, being considerably longer than the systolic. The changes in arterial pressure with each heart beat are diagrammed in Figure 18-10 (upper portion). The highest level reached is the systolic pressure, and the lowest pressure reached is the diastolic pressure. These pressures in the normal subject at rest are usually around 120 and 80 mm. of mercury

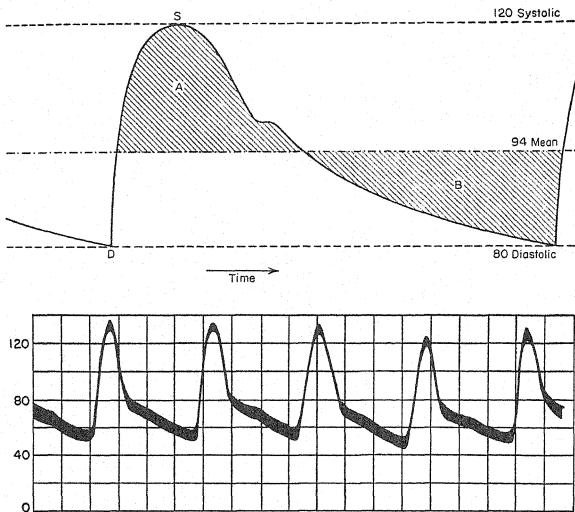


Figure 18-10. Arterial pressure curves.

Above, diagram of changes in pressure in the aorta during a cardiac cycle. See text for further explanation. *Below*, pressure record obtained directly from the lumen of the femoral artery by means of a large hypodermic needle connected with a Sanborn electromanometer.

respectively. The pressure indicated above would be written as 120/80 and would be referred to verbally as "120 over 80." The difference between systolic and diastolic pressure is called the *pulse pressure*; for example, $120 - 80 = 40$ mm. of mercury pulse pressure. It is necessary sometimes to consider mean arterial pressure rather than systolic or diastolic. The

mean pressure is represented by a line drawn through the actual arterial blood pressure curves at a level such that the enclosed area above the line equals the enclosed area below the line.

Use of the mercury manometer. The mercury manometer is used extensively for direct recording of blood pressure in the physiological laboratory. This instrument, which is a U-tube type of manometer, is one of the simplest devices for measuring pressure. If water is placed in a U tube as illustrated, the level on the left will be the same as the level on the right, since each side is subjected to the atmospheric pressure. If one blows on the right or applies pressure from any source, the level of the liquid on the right will be depressed and the level

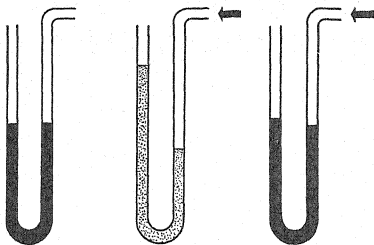


Figure 18-11. Recording of pressure by means of U-tube manometer.

A, Manometer filled with mercury, no pressure applied. B, Manometer filled with water and a given pressure applied. C, Manometer filled with mercury and the same pressure applied as that used in B. Change in level in C is $1/13.6$ as great as in B, since mercury is 13.6 times as heavy as water.

on the left will be correspondingly lifted as illustrated. The distance between the two levels is directly proportional to the pressure being applied and is usually measured in centimeters ($2.54 \text{ cm.} = 1 \text{ inch}$). Thus, if the distance is 13.6 cm., the pressure is said to be 13.6 cm. of water. In other words, this is the pressure required to support the weight of a column of water 13.6 cm. high, or it is the pressure exerted at the bottom of a column of water of this height. The diameter of the tube does not influence the reading; the tubing may be of any convenient size. Now, if mercury, which is a liquid that is 13.6 times as heavy as water, is placed in the U tube and the same pressure illustrated in Figure 18-11 is applied to the mercury, the distance between the two levels will be only 1 cm. or 10 mm. The pressures in the arterial tree in man and animals are such that a water manometer of sufficient length to record them would be of inconvenient size. Therefore, a mercury manometer is used and the pressures are expressed as millimeters of mercury. These can be converted to

centimeters of water by dividing by 10 (to convert millimeters to centimeters) and multiplying by 13.6 (to convert centimeters of mercury to centimeters of water).

$$\text{mm. of mercury} \times \frac{13.6}{10} = \text{cm. of water}$$

Therefore, mm. of mercury $\times 1.36 = \text{cm. of water}$,

$$\text{and } \frac{\text{cm. of water}}{1.36} = \text{mm. of mercury}$$

Mercury, being a heavy liquid, will not follow pressure changes occurring rapidly. For example, if the actual arterial blood pressure is 120/80 and is being recorded directly in the experimental animal by a cannula connecting the artery with the manometer, the excursions of the mercury may be only one fourth as great, or 10 mm. Although no actual reading of systolic or diastolic pressure is obtained when the mercury manometer is used, mean pressures can be determined rather closely. Under most conditions, as pulse pressure changes, the magnitude of the excursions of the mercury level will change in the same direction, so that one has an index of changes in pulse pressure. The curve shown in the lower part of Figure 18-10 is taken by a newer type of recording device which can respond rapidly, so that actual pressures are obtained throughout the cycle. From such a record, systolic and diastolic pressures can be read and mean pressure can be calculated.

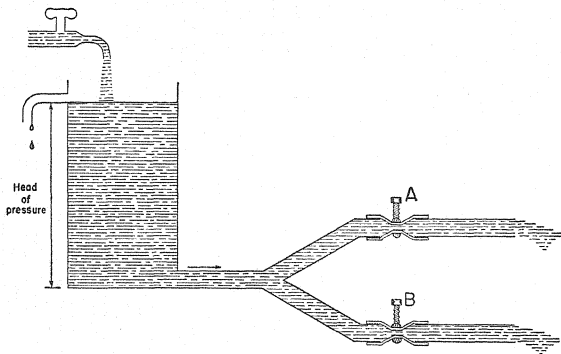


Figure 18-12. Schema to illustrate alteration of flow of blood to organs by changes in resistance imposed by arterioles.

(From Youmans' *Basic Medical Physiology*.)

Advantages of adjustable arteriolar tonus. An arterial pressure of the relatively high level seen in mammals combined with adjustable resistance to flow, through alterations in arteriolar tonus in the various organs, makes possible the shunting of blood away from the organs that are less active to those which are more active. This may be illustrated as follows. A reservoir is kept filled to a certain level with water, as shown in Figure 18-12, so that the head of pressure for producing flow remains constant. The liquid flows through a Y tube, each branch of which is connected to a section of glass tubing by means of a piece of rubber tubing, and a clamp is placed on each piece of rubber tubing, so that the size of the lumen may be adjusted. The clamps correspond to the smooth muscle in the arterioles, and the capillary bed supplied by the "artery" is considered arbitrarily as consisting of two portions. In the figure, the clamps are shown as being set to produce identical resistances; therefore, regardless of the amount of blood that flows in the "artery" per minute, one-half will pass through each branch. If, now, clamp A is tightened and clamp B is loosened, a new situation can be produced in which the amount of flow in the "artery" is unchanged, but one-fourth of the fluid is passing through A and three-fourths through B. Thus, a 50 per cent increase in the fluid flow through B is obtained by redistributing the flow in the absence of any change in the head of pressure.

From this preliminary description of the circulatory system, the student should understand that the pressures and flow of blood are determined primarily (1) by the pumping action of the heart, and (2) by the resistance to the flow of blood through the arterioles. Pressure, volume, and flow in the larger vessels, namely, the arteries and veins, become altered secondary to changes in either cardiac output or peripheral resistance.

Chapter 19

HEART MUSCLE AND THE HEART BEAT

Physiological Anatomy of the Heart

21140
The shape and position of the human heart in the standing subject can be indicated by the right-hand fist held downward, the thumb side being to the left (see Figures 19-1 and 19-2). The end of the thumb corresponds to the apex of the heart which lies on the left leaf of the diaphragm. The beat of the heart may be felt at the apex, which is normally between the fifth and sixth ribs (fifth intercostal space), approximately on a line extended down from the midpoint of the left clavicle. The shape of the human heart can be observed under the fluoroscope, or permanent films can be obtained. Also, the heart can be outlined by percussing the chest. This is possible because the part of the thoracic wall which overlies the air-containing lung tissue is resonant and a duller note is obtained over the part of the thoracic wall which is in contact with the heart.

The heart lies in a loose-fitting sac, the *pericardium*, which is composed of fibrous connective tissue and lined with a smooth serous membrane. The serous membrane which is reflected to cover the surface of the heart is called the *epicardium*. These two layers also are known as *parietal* pericardium and *visceral* pericardium. In Figure 19-3, a ventral view of the heart is shown with the parietal pericardium reflected and the surface of the heart exposed. The space between the two layers of pericardium allows for expansion and contraction of the heart and is filled with a small amount of pericardial fluid which serves as a lubricant.

The muscular walls of the heart are known as the *myocardium*, and the layer of squamous epithelium lining the chambers of the heart is called the *endocardium*. The human heart, as in other mammals, consists of two auricles or atria and two ventricles. The left ventricle has the thickest wall, the right ventricular wall is next in thickness, and the atria have fairly thin walls. The thickness of the walls shows a direct relationship

to the amount of work done by the chambers. Also, if a condition develops in which a given chamber is subjected chronically to an increased load, the musculature of the walls of that chamber will undergo hypertrophy. This is analogous to the hypertrophy of skeletal muscle which is produced by exercise.

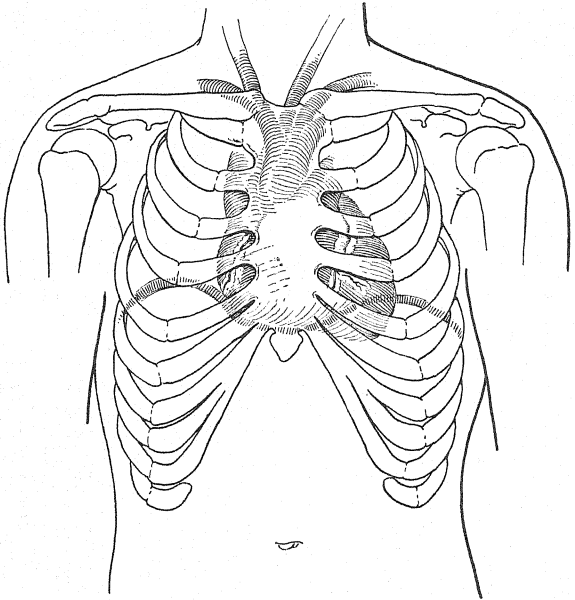


Figure 19-1. Location of heart with reference to thorax.

The heart is equipped with four valves which permit flow of blood from auricles to ventricles and from the ventricles into the arteries, and prevent flow in the reverse direction. These valves are composed of two or three cusps which become filled with blood, so that the margins of the cusps are thrown together and close the orifice as a backflow begins

when the pressure "upstream" decreases below the pressure beyond the valve. The valve between the left auricle and left ventricle is known as the *mitral* valve or *bicuspid* valve. It consists of two cusps or leaflets which are prevented from being forced back into the auricle during the

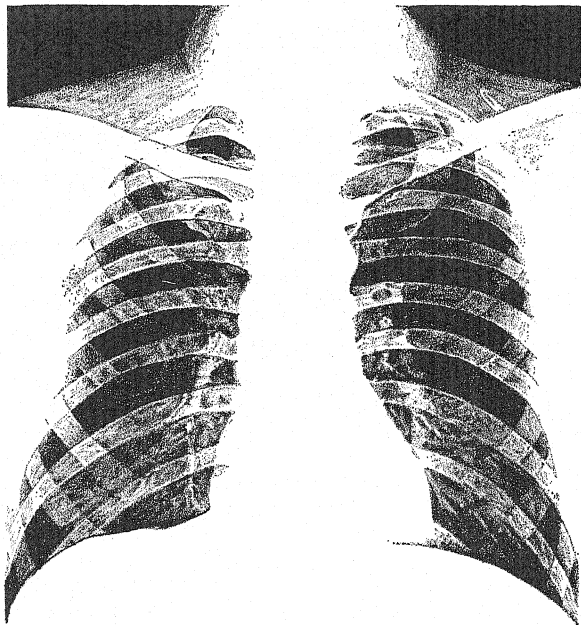


Figure 19-2. Heart as seen by fluoroscope.

Drawing made from X-ray film.

ventricular contraction by several tendinous cords (*chordae tendineae*) which pass from the leaflets of the valves to projections of the myocardium called papillary muscles. The opening between the right auricle and right ventricle is equipped with three cusps which is the basis for the name,

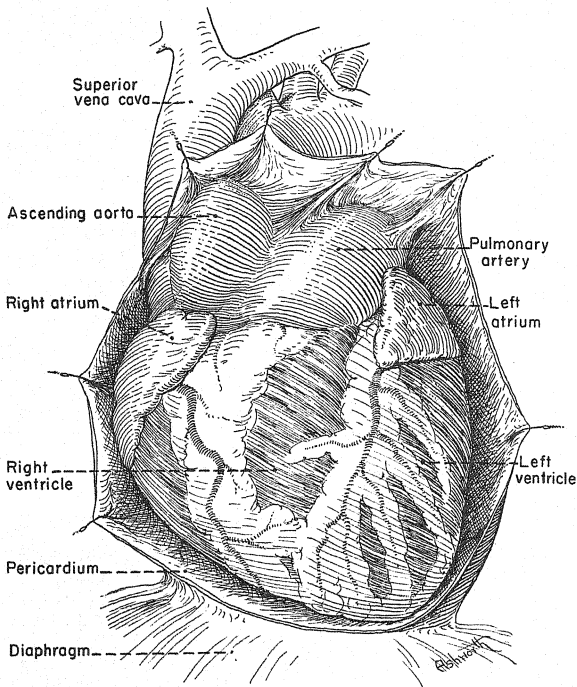


Figure 19-3. Heart with pericardium reflected.

tricuspid valve. Otherwise it is similar in structure to the mitral valve. The auriculoventricular valves prevent backflow into the auricles during contraction of the ventricle. At the base of the aorta where it connects with the left ventricle and at the base of the pulmonary artery where it joins the right ventricle, are located the aortic and the pulmonic valves respectively. Each of these consists of three half-moon shaped flaps, giving rise to the name *semilunar* valves. These valves prevent reflux of blood

from the aorta and pulmonary arteries back into the ventricles during diastole.

The wall between the left auricle and right auricle is called the interauricular septum, and the wall which separates the right and left ventricles is called the interventricular septum. Normally, there is no opening

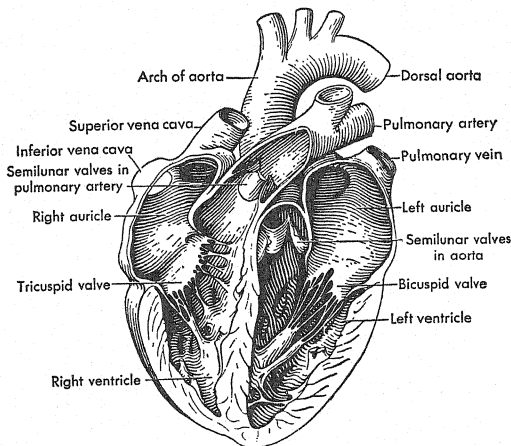


Figure 19-4. Dissection of heart, anterior view.

(By permission from Haggard, *The Science of Health and Disease*. Copyright, 1938, by Harper and Brothers.)

in these septa, but in congenital malformation of the heart there may be either an interauricular or an interventricular septal defect. In the fetus, there is an opening between the two auricles, the *foramen ovale* (see fetal circulation, page 429).

Automaticity of the Heart

The heart of a vertebrate animal will continue to beat and the chambers will be activated in normal sequence for minutes or even hours after it is removed from the body and placed in, or perfused with, an appropriate

solution. This demonstrates that the structures necessary for the initiation of the impulse and for its spread to the musculature of the cardiac chambers are present within the heart itself. Although the heart, like other visceral organs, is supplied with extrinsic nerves, these nerves serve to regulate the rate and strength of the heart beat, and are not necessary for the initiation or conduction of the impulse or for the contraction of cardiac muscle.

Since the physiology of the heart of amphibians and reptiles resembles, in many respects, that of the mammalian heart, the frog or turtle heart

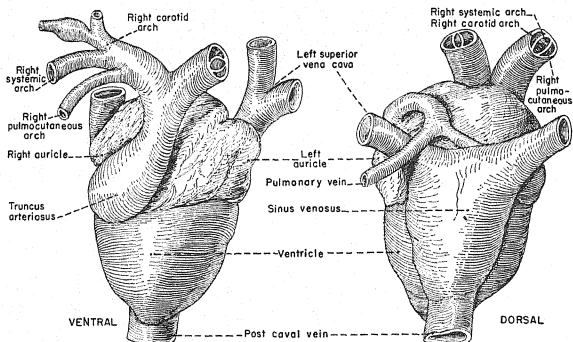


Figure 19-5. Frog heart and major vessels.

has been used extensively for research and for student laboratory experiments. The frog heart, shown in Figure 19-5, consists of a *sinus venosus* (a venous sac) formed by the junction of three large veins which bring blood from the anterior and posterior parts of the body. These veins are the two superior and one inferior *venae cavae*. The venous blood flows from the sinus venosus into the right auricle, and the left auricle receives blood from the lungs. The one ventricle receives blood from the two auricles and pumps the blood into the *truncus*, or *bulbus*, *arteriosus* which immediately divides into two branches. In the turtle, there is also a distinct separation between sinus venosus, auricles, and ventricle (Figure 19-6).

In exposed frog and turtle hearts, one may observe that the thin-walled sinus venosus contracts first, then the auricles contract, and lastly the ven-

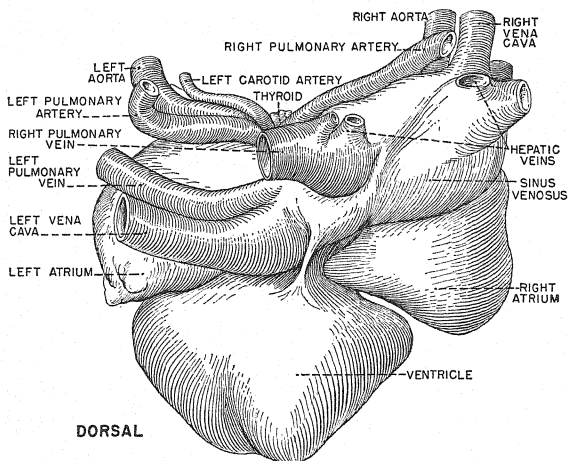
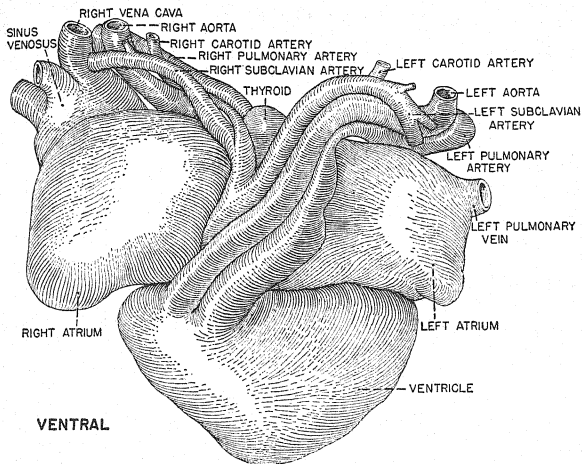


Figure 19-6. Turtle heart and major vessels.

tricle contracts. Then there is a period of quiescence until the next contraction of the sinus venosus. If a thread is tied tightly around the junction between the sinus venosus and auricles, the sinus venosus continues to beat at a rate similar to that observed before the ligature was tied. The auricles and ventricle commonly stop for a brief period immediately after the ligature is tied; then, usually, they resume beating at a rate somewhat slower than the rate of the sinus. If now a second ligature is tied around the heart between the auricles and ventricle, the auricles will continue to beat and the ventricle usually will cease to beat for a short period, after which it may resume beating at a rate slower than the rate of the auricles (Figure 19-7). If the lower portion of the ventricular musculature is cut

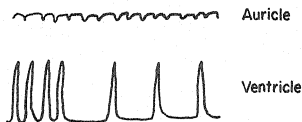


Figure 19-7. Production of block by means of a ligature around the auriculo-ventricular groove.

Turtle heart; upper record, auricular contractions; lower record, ventricular contractions.

away from the remainder of the heart, ordinarily, it will not beat “spontaneously” but it may be made to contract in response to artificial stimuli. These experiments illustrate that the impulse which initiates the heart beat normally originates in the sinus venosus and is conducted to the auricles and then to the ventricle, causing the chambers of the heart to contract in sequence. If, however, the conduction from sinus to auricles is prevented, an impulse can originate in the auricles and this will spread to the ventricle. The impulse is initiated less frequently in the auricles than in the sinus venosus; consequently, under normal conditions, the impulse coming from the sinus activates the auricles before an impulse has time to develop in the auricles. Likewise, an impulse may develop in the ventricle, in the absence of activation, by impulses coming from the auricles.

Properties of Heart Muscle

Although under physiological conditions the musculature of the ventricles is activated by impulses reaching it over the specialized conducting system, described below, any portion of the cardiac muscle can be acti-

vated directly by electrical stimulation. Furthermore, any stimulus which is of sufficient strength to cause a response in the heart muscle will spread over the entire mass of muscle, and hence will produce a contraction just as great as that produced by any considerably stronger stimulus. This is a manifestation of the *all-or-none law*. It will be recalled that submaximal stimuli applied to skeletal muscle are capable of causing contraction of some of the fibers of the muscle without influencing other fibers located farther from the stimulating electrodes. No such submaximal responses can be obtained from the ventricles of the heart, since the impulse once set up will spread to all of the muscle cells of the ventricle. When cells are as intimately interconnected as they are in heart muscle, they are

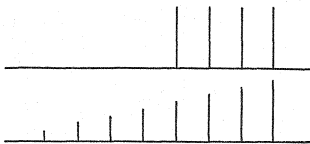


Figure 19-8. All-or-none response of heart muscle.

Upper record indicates amplitude of contraction of turtle ventricle. Lower record indicates strength of electrical stimulus.

said to form a *syncytium*. In Figure 19-8 it is illustrated that a barely effective stimulus produces a contraction of the same magnitude as that produced by stronger stimuli. Although the strength of contraction of heart muscle is independent of the strength of the stimulus, there are factors which determine how strong the stimulus must be in order to be effective and there are still other factors which will influence the strength of the contraction.

The heart muscle, once activated, recovers its irritability over a definite time period. During a brief period, corresponding to the contraction phase, heart muscle will not respond to a second stimulus regardless of the intensity; then, during the period of relaxation, the heart muscle will respond to stimuli which are stronger than those normally required. The recovery periods are known respectively as the *absolutely refractory period* and the *relatively refractory period*. The refractory periods may be studied in the turtle or frog heart by letting the heart beat spontaneously and then applying an artificial stimulus at various points during diastole and systole. In Figure 19-9 records obtained in such a study are reproduced. It will be noted that the contraction elicited during the rela-

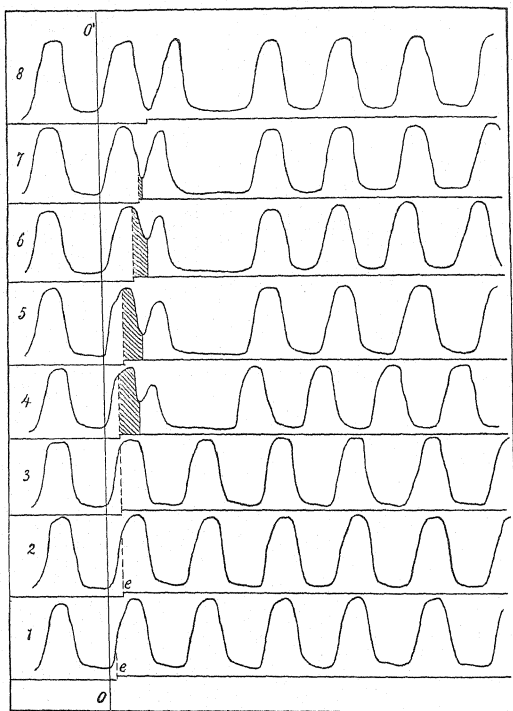


Figure 19-9. Effect of electrical stimulus, applied at different times during systole and diastole.

This is a record of contractions of a frog heart. In 1, 2, and 3, the stimulus (*e*) falls during refractory period and has no effect. In 4-8 the stimulus elicits a premature ventricular contraction followed in each instance by a compensatory pause. The latent period between stimulation and contraction is shorter the later the stimulus is applied in diastole. (Reproduced by permission from Howell, *Textbook of Physiology*. Copyright, 1940, by W. B. Saunders Co.)

tively refractory period is of less amplitude than the normal contractions. Also, a *compensatory pause* follows the artificially elicited "premature" beat because the next normal impulse conducted down from the atria finds the ventricle refractory.

The Conducting System

Histological studies of the heart reveal that in addition to the muscle cells there are bundles of tissue of another type. There is an intricate network of these bundles which are concerned with the conduction of impulses. It should be realized that cardiac muscle fibers themselves will conduct impulses, and the main advantage of the specialized conducting system is that it makes possible the rapid spread of the excitation throughout the two ventricles, so that the entire mass of muscle is activated almost synchronously. The result is a more synchronous and efficient pumping action than is achieved when excitation occurs at only one point in the ventricle, as by electrical stimulation at this point.

The specialized system for initiating the impulse in the human heart and for conducting the impulse to the ventricles consists of a *sinoauricular node* (abbreviated S-A node) located at the junction of the superior vena cava with the right auricle, and an *auriculoventricular*, or A-V, node which lies near the base of the interauricular septum. The A-V node gives rise to the auriculoventricular bundle and its arborizations. The auriculoventricular bundle runs along the interventricular septum, then divides into right and left branches which pass down on each side of the interventricular septum. Each branch divides again and again to form an intricate network over the inner surface of the ventricular cavity, and small branches pass out through the musculature toward the outer surface of the heart.

Under normal conditions, the impulse originates in the sinoauricular node and spreads throughout the auricular musculature. Then the impulse reaches the auriculoventricular node and is conducted down over the bundle and branches so that it is spread to the entire ventricular musculature. Actually, there is a difference of a few hundredths of a second between the time of arrival of the impulse at various points on the surface of the heart.

If an artificial stimulus is applied either to the sinoauricular node or to the auricular musculature, at a time when the tissue is not refractory,

an impulse will spread throughout the auricles and will be picked up by the auriculoventricular node and conducted through the ventricle, just as if it had originated "spontaneously" in the S-A node. Also, a stimulus applied to the muscle of the right or left ventricle will cause an impulse to spread over the entire ventricular musculature, but, commonly, will not pass up the auriculoventricular bundle to reach the auricles. However,

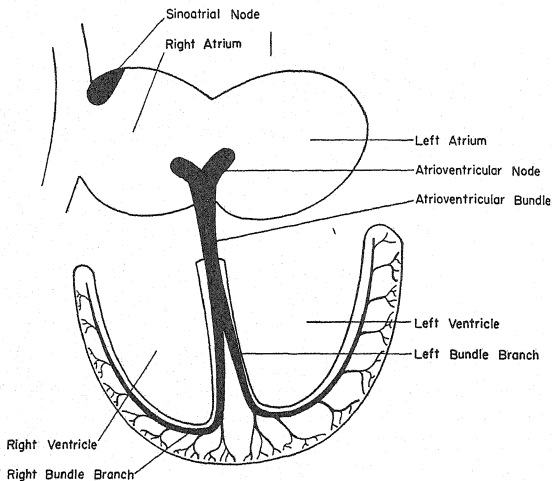


Figure 19-10. Diagram of the specialized conducting system of the heart.

(From Youmans' *Basic Medical Physiology*.)

an impulse originating in the auriculoventricular bundle will pass up and spread over the auricles, as well as in the normal direction to the ventricular musculature.

Effects of temperature. The rate of discharge of the sinoauricular node is influenced by temperature. This can be demonstrated by applying the surface of a test tube containing either hot or cold water directly to the exposed node. Cooling the S-A node causes slowing of the heart rate and, if severe, may displace the pacemaker to the A-V node. Warming causes an increase in rate. In man, the body temperature normally remains con-

stant; however, an increase of four or five degrees may occur in disease. Fever characteristically causes an elevation of the heart rate, the increase in rate being about nine or ten beats per degree of fever, but only a fraction of this increase in rate can be attributed directly to the increased temperature of the S-A node. At the same time, the rate of metabolism of the body is elevated and the heart rate is affected by indirect mechanisms.

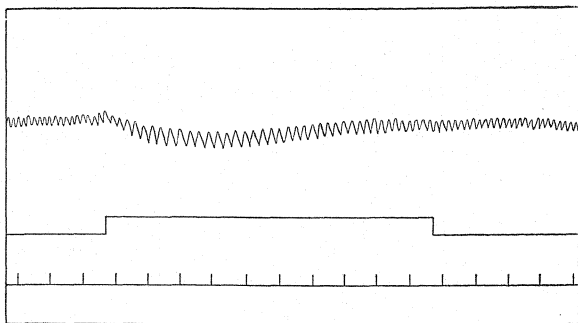


Figure 19-11. Effect on heart rate of cooling of sinoauricular node.

Upper tracing shows a mercury manometer record of blood pressure and heart rate of a dog with thoracic cage opened to expose the heart. The lower record indicates time in 5-second intervals. At the time indicated by the middle record, the end of a test tube containing ice water was applied directly to the sinoauricular node. Heart rate decreased from 72 to 44 beats per minute.

Effects on the heart of calcium and potassium ions. The solutions used for maintaining the beat in the isolated heart of the frog, turtle, or mammal have a comparatively simple composition. For frogs and turtles, Ringer's solution is used, and Locke's solution is employed for perfusion of mammalian hearts.

RINGER'S SOLUTION *

0.650% NaCl
0.012% CaCl_2
0.014% KCl
0.020% NaHCO_3
0.001% NaH_2PO_4
0.200% Glucose

LOCKE'S SOLUTION *

0.9% NaCl
0.024% CaCl_2
0.042% KCl
0.02% NaHCO_3
0.1% Glucose

* For most experiments in the physiological laboratory, the glucose can be omitted from these solutions. If this is done, the solutions will keep for long periods.

The viability, irritability, and contractility of the isolated heart can be maintained for hours by means of solutions as simple as those shown above. The essential features of these solutions are (1) the presence of Na, Ca, and K ions; (2) the presence of bicarbonate or phosphate in amounts sufficient to produce a pH slightly on the alkaline side; (3) the presence of an organic compound, such as glucose, to serve as a source of energy; and (4) a total osmotic tension similar to that of the interstitial fluid. Also, it is essential that the solution be well oxygenated. Considerable variations in the amount of most of the constituents are possible. Either the calcium or the potassium content of the solution can be altered considerably *if the amount of the other ion is proportionately altered*. If the *ratio* of Ca ions to K ions in the solution is significantly altered, striking changes in the rate and contractility of the perfused heart are seen. A considerable increase or decrease in the Ca/K ratio causes a decrease in rate. In other words, there is an optimal ratio for maintaining the heart rate. An excess of Ca causes shortening of the muscle fibers and, finally, cardiac arrest in a contracted state. Excess K causes a decrease in heart rate and, if severe, cardiac arrest with the muscle in a relaxed state. The balance between Na, Ca, and K ions is important in maintaining the normal semipermeable state of the membranes of the cells which compose irritable tissues, and this state in turn makes possible the normal polarization. An excess of K (decrease in the Ca/K ratio) seems to favor depolarization and an excess of Ca seems to make depolarization more difficult. Thus, in general, K excess or Ca deficiency predisposes to an increased irritability, and Ca excess or K deficiency contributes to a decreased irritability of all of the irritable tissues.

Action Currents in the Heart

The passage of the impulse over cardiac muscle fibers, as in the case of nerve and skeletal muscle, is associated with changes in polarization similar to those described for axons and skeletal muscle fibers. However, in the case of the heart, one is dealing with a large and intricately arranged mass of muscle which is being activated almost simultaneously at numerous points. Since the body is a conductor of electricity, the electrical field produced by the spread of the cardiac impulse can be detected by connecting almost any two points on the body surface in a circuit which includes a sensitive device for recording current. A characteristic pattern of electrical changes, known as the *electrocardiogram*, is

obtained; the instrument used for this purpose is called an electrocardiograph. A normal electrocardiogram, as seen, for example, when the electrodes, or leads, are placed on the right arm and left leg, is illustrated in Figure 19-12.

The scale indicates intensity vertically and time horizontally. The waves are labeled P, Q, R, S, and T as shown; P, R, and T are upward deflections and Q and S downward deflections.

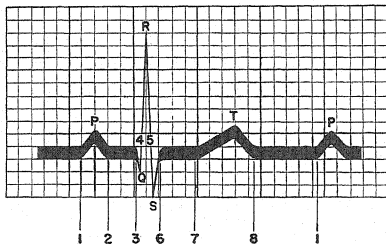


Figure 19-12. Diagram of normal electrocardiogram as seen in standard lead II.

P wave: section of record from point where it leaves isoelectric level at 1 until it returns at 2. Q wave: section of record from point 3 where it leaves isoelectric level to point 4 where it returns to this level. R wave: section of record from point 4 where it leaves isoelectric level to point 5 where it returns to this level. S wave: section of record from point 5 where it leaves isoelectric level to point 6 where it returns to this level. S-T segment: section of record from line 6 to line 7. T wave: section of record between lines 7 and 8. T-P interval: isoelectric period extending from the end of the T wave to beginning of the P wave. (From Youmans' *Basic Medical Physiology*.)

The P wave occurs just before the auricle contracts; it is the electrical change associated with passage of the impulse over the auricular musculature. The QRST complex, i.e., the portion of the record from Q to the end of T, is the electrical change associated with spread of the depolarization over the ventricular muscle and the return of polarization of the ventricle. It corresponds temporally with the contraction and relaxation of the ventricle. During the period from the end of the T wave to the next P wave, the musculature of the auricles and ventricles is polarized and in a resting state. The duration of this interval shows wide variations with changing heart rates, whereas the duration of the P wave and QRST complexes show minor alteration with changes in heart rate.

Efferent Nerves of the Heart

The initiation and conduction of the cardiac impulse and the cardiac contraction can occur in the absence of the efferent nerves to the heart. The cardiac nerves have a regulatory function; they influence the rate of initiation of impulses, the rate of conduction of the impulse, and the strength of the contraction and irritability of cardiac muscle.

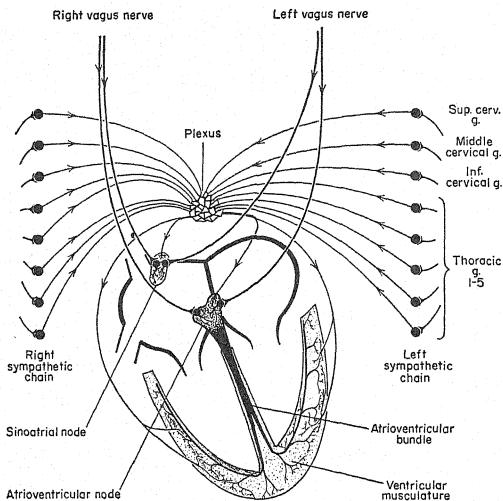


Figure 19-13. Diagram of innervation of conducting system of the heart.

The conducting system has a dual innervation, as diagrammed. Cholinergic fibers supplied exclusively by the vagus, which is a part of the parasympathetic system, have an inhibitory action on the sinoauricular and auriculoventricular nodes. Adrenergic fibers, supplied largely by the thoracolumbar system, have an excitatory action on the S-A and A-V nodes and on the terminal portion of the conducting system or directly

on the cardiac muscle. Thus, a decrease in the rate of impulse formation in the sinoauricular node and in rate of conduction of the impulse may be produced by an increased activity of the vagal fibers, and an increase in rate of "discharge" of the sinoauricular node and in the rate of conduction of the impulse is produced through an increased activity of the sympathetic nerves. Under physiological conditions, these nerves frequently are reciprocally influenced, one set showing decreased activity as its antagonist shows increased activity.

Some of the effects of the vagus nerves on the conducting system of the heart are related to the fact that the sinoauricular node is supplied more effectively by the right vagus than by the left vagus. The vagus nerves coming down from the brain can be exposed at the cervical level in anesthetized animals and sectioned. Then, if one stimulates the distal end of the sectioned right vagus

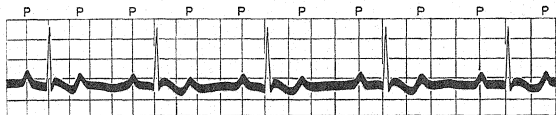


Figure 19-14. 2:1 aurioventricular block.

Alternate auricular contractions, indicated by P waves, are not followed by ventricular contractions.

nerve, a severe inhibitory influence is produced in the sinoauricular node with only mild inhibition of the auriculoventricular node. The sinoauricular node ceases to serve as the site of impulse formation and the auriculoventricular node takes over the task of initiating the impulse. The impulse can pass up over the auricles from the auriculoventricular node and activate the auricles even before it has had time to pass over the ventricular conducting system to activate the ventricles, but the interval between auricular and ventricular contraction (P-R interval of the electrocardiogram) is considerably shortened. If the distal end of the sectioned left vagus nerve is stimulated, the inhibitory influence predominately concerns the auriculoventricular node. This inhibition is expressed, not as a complete failure of the node to respond, but by a prolongation of the period required for it to regain irritability; therefore, the A-V node responds to every second or third impulse initiated by the sinoauricular node. Thus, alternate QRST complexes may fail to appear in the electrocardiographic record (Figure 19-14). This is a type of *heart block*.

The heart of the frog or turtle may be kept quiescent for considerable periods by electrical stimulation of the vagus. In mammals, vagal stimulation produces a period of asystole, then the heart begins to beat again

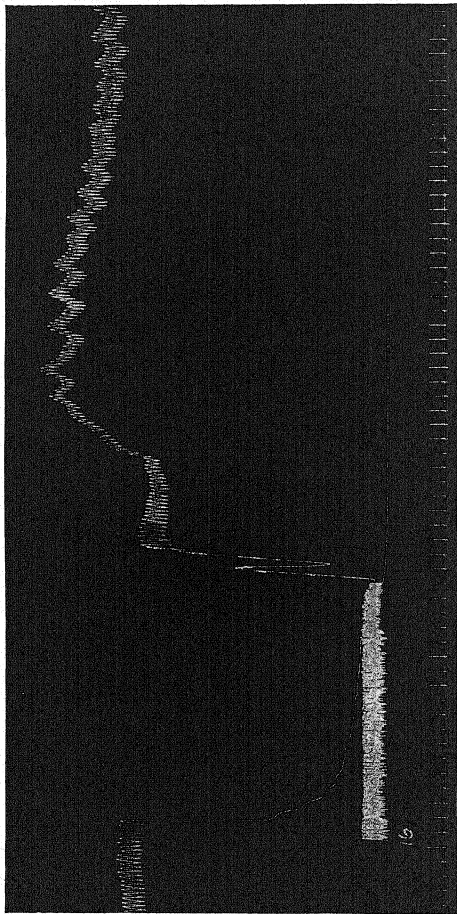


Figure 19-15. Production of cardiac arrest by stimulation of the peripheral end of the sectioned vagus nerve in the dog. Blood pressure and heart rate are shown in the upper tracing; a 16-second period of tetanizing stimulation is indicated by the middle line, and time in 1-second intervals by the bottom tracing. The sharp rise in pressure seen at the right, beginning about 9 seconds after the heart beat was restored, is attributable to epinephrine released from the adrenal medulla during the fall in blood pressure but which could not reach the heart and arterioles of the systemic circuit until several seconds after the circulation was restored.

at a slow rate, even though the stimulation is maintained. Injection of acetylcholine into a vein in sufficient amounts produces cardiac arrest for a brief period, after which the heart beat appears at a rate faster than the control level and blood pressure gradually is restored (Figure 19-16).

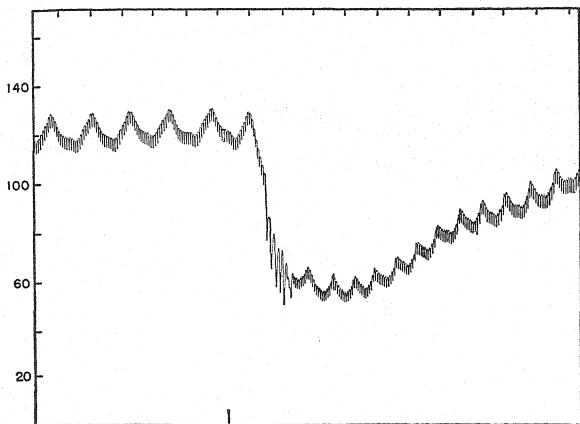


Figure 19-16. Effect on heart rate and blood pressure following intravenous injection of acetylcholine.

The acetylcholine (1.5 mgm.) was injected as rapidly as possible at the time indicated by the upstroke on the bottom line. At the top of the record, time is shown in 5-second intervals. The immediate effects on blood pressure and heart rate are similar to the effects of vagal stimulation, but the recovery to the control levels following injection of acetylcholine is considerably more gradual. The figures on the left indicate the pressure scale in millimeters of mercury.

The inhibitory effects of vagal stimulation and of acetylcholine on heart rate can be greatly potentiated if the cholinesterase in the heart is inactivated by the injection of *eserine*. This drug blocks the action of the enzyme, so that the acetylcholine which is produced in the sinoauricular and auriculoventricular nodes during vagal stimulation will persist in effective amounts for a longer period. Whereas vagal stimulation will not maintain cardiac arrest, ordinarily, it may cause cessation of the heart

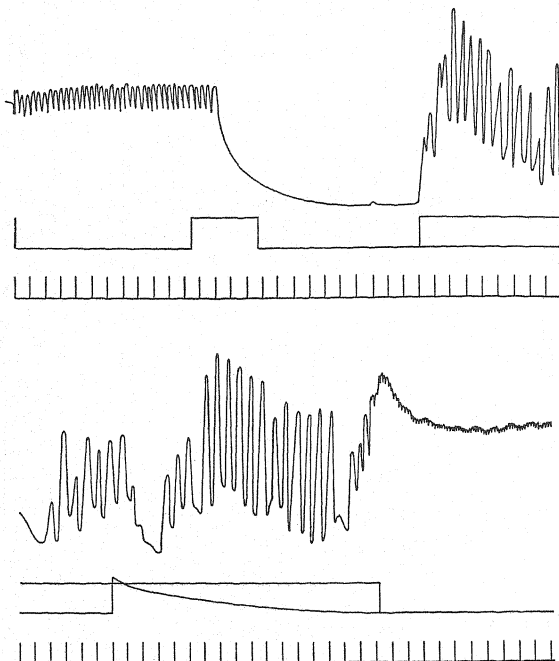


Figure 19-17. Use of drugs to influence the cardioinhibitory effect of vagal stimulation.

In the upper record cardiac arrest is produced by stimulation of the peripheral end of the sectioned vagus in a dog which has received eserine, a compound which blocks the action of cholinesterase and thus protects acetylcholine from destruction. To the right of the upper record cardiac massage was commenced and was continued in the lower record. At the time indicated by the upstroke at the left of the lower record atropine was injected intravenously. After about 16 seconds the heart began to beat and cardiac massage was discontinued. Time is shown in 1-second intervals by the lowermost tracing on each record.

beat in the eserinizated animal. This is illustrated in Figure 19-17. If the circulation is maintained by cardiac massage, the heart beat can be restored by the injection of atropine which makes the cardiac conducting system unresponsive to the action of acetylcholine. After atropinization, neither acetylcholine nor vagal stimulation is capable of causing a decrease in heart rate.

The cardiac muscle is directly influenced little or none by the vagal innervation, but does receive an excitatory adrenergic innervation from the sympathetic system. Sympathetic stimulation produces an increased strength of ventricular contraction and, through its effects on irritability, predisposes to premature ventricular contractions.

Irregular Heart Action

There are many types of irregularity of heart action related to disturbances in the origin or conduction of the cardiac impulse. These are known as *arrhythmias*. In normal subjects, there is waxing and waning of the heart rate with each respiratory cycle, and the *respiratory arrhythmia* is more pronounced, the slower and deeper the breathing. Abnormal rhythms are of three main categories: *block*, *ectopic beats*, and *fibrillation*.

Heart block refers in general to any arrhythmia in which there is impairment of conduction of the impulse over the specialized conducting system. The locus of the block may be such that the impulse fails to spread from the sinoauricular node, or conduction by the A-V node may fail, or the block may occur in one of the bundle branches.

Ectopic beats or series of beats are produced when the cardiac impulse originates at a focus outside of the normal site. This may occur on an *escape* basis when the upper parts of the conducting system are subjected to inhibitory influences, as from stimulation of the right vagus nerve (page 223); or, on the other hand, *hyperirritability* may develop at any site, so that the ectopic focus usurps the role of pacemaker. Depression of the sinoauricular node by reflexes which activate the vagal cardioinhibitory pathway may cause the pacemaker to be displaced to the A-V node or bundle or even to the bundle branches. The pacemaker cannot be displaced farther down than this, since the vagus does not innervate the lowermost portion of the conducting system. Ectopic beats on the basis of a hyperirritable focus may arise from any part of the auricles or ventricles.

They are referred to as premature beats. Occasional premature beats, or extrasystoles, originating in either the auricles or ventricles occur commonly in normal persons. The premature beat frequently is followed by a longer than normal diastolic interval, or *compensatory pause*, because the next impulse coming from the S-A node may encounter a refractory state in the ventricles.

Auricular fibrillation. In this condition, there is no coordinated auricular systole. When one directly observes the fibrillating auricles, he sees a shimmering, undulating type of movement. Instead of virtually simultaneous contraction followed by relaxation of the entire auricular musculature, some fibers are contracting while others are relaxing. Apparently, impulses are able to find their way about in muscle fibers that have recovered suf-

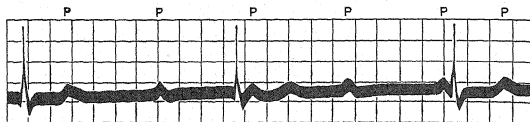


Figure 19-18. Electrocardiogram showing complete auriculoventricular block.

P waves, indicating auricular contractions, are independent of ventricular complexes and occur at a more rapid rate.

ficiently from previous contractions so that they can respond again. Thus, the fibrillatory activity is perpetuated by impulses passing in one or more circuitous paths. Numerous impulses reach the A-V node, and this structure conducts an impulse again as soon as it has recovered sufficiently from the previous response. Characteristically, the ventricular systoles are considerably more frequent than the normal, and the intervals between the systoles are completely irregular. In the experimental animal, a condition simulating auricular fibrillation can be produced by very rapid electrical stimulation of any site in the atria. The erratic arterial blood pressure caused by this procedure is illustrated in Figure 19-19. Typically, the normal auricular rhythm is re-established very quickly after cessation of the electrical stimulation.

Auricular fibrillation is compatible with life, since auricular systole is not important for producing filling of the ventricles in man and since the pumping action of the ventricles continues; however, the fast ventricular rate seen in auricular fibrillation is disadvantageous.

Figure 19-19. Effects on blood pressure of auricular fibrillation and ventricular fibrillation.

On the left of the record the left atrium was stimulated with "tetanizing" current producing auricular fibrillation. At the right the same stimulus was applied directly to the ventricular muscle and ventricular fibrillation was produced. Note that the blood pressure falls as sharply as from cardiac arrest and reversion to normal rhythm does not occur after cessation of the stimulation. Time is shown by the lower tracing in 1-second intervals.

Ventricular fibrillation. Direct electrical stimulation of the ventricles will set up the same incoordinated type of contraction that is described above for the auricles. However, two striking differences are seen in the blood pressure record when the effects of auricular and ventricular fibrillation are compared. In the first place, the arterial pulse disappears instantly when ventricular fibrillation is initiated. That this would be true is evident when one considers that the pumping action of the heart is accomplished by means of rhythmic contraction and relaxation of the ventricular muscle, and a sustained contraction of any degree could not be expected to produce pulsation any more than would occur from sustained relaxation of the ventricles. Second, the ventricles do not spontaneously revert to normal rhythm, once the fibrillation is established. In fact, a single electric shock applied to the ventricle at the right phase of the cardiac cycle may set up ventricular fibrillation, and normal rhythm will not be restored unless special methods are employed. During ventricular fibrillation, the auricles continue to beat rhythmically, and the circulation can be maintained by cardiac massage, if the heart is exposed, while attempts are made to stop the fibrillation. When the fibrillation of the ventricles is stopped, as by means of a strong electric current applied briefly to the entire heart, the sinoatrial node resumes the role of pacemaker.

Chapter 20

RATE AND STRENGTH OF THE HEART BEAT

The demands upon the heart vary greatly, depending upon the amount of skeletal muscular activity. The quantity of blood which the heart must pump per minute is related closely to the metabolic requirements of the body, and the changes in cardiac output which occur with alterations in metabolism are accomplished through changes in both rate and strength of the heart beat. The major mechanisms by means of which these adjustments occur will be described in this chapter.

Ventricular Volume and Pressure

Each cardiac chamber undergoes cyclic changes in its volume and in the pressure within it. During systole, the pressure in the chamber increases and the volume decreases as blood is expelled, and during diastole, the pressure decreases and volume increases.

Left ventricular pressure curve. In Figure 20-1, it is illustrated that the pressure in the left ventricle is near the atmospheric pressure level during diastole. This is true because the holding capacity of the left ventricle is such that the amount of blood which flows into it during a diastolic period of average length is not sufficient to fill the ventricle enough to cause any considerable increase in pressure above the atmospheric level. At the end of the period of diastole, the auricles contract, but the auricular contraction in mammals is a minor factor in the filling of the ventricles. The contraction of the ventricles begins within about a tenth of a second after the onset of auricular contraction. The pressure in the left ventricle rises sharply during ventricular systole and at the beginning of this rise in pressure the auriculoventricular valves are thrown shut and serve to prevent the reflux of blood into the atrium throughout the period when the pressure in the ventricle exceeds that in the atrium. As the pressure

continues to rise rapidly in the left ventricle, it soon reaches and exceeds the pressure in the aorta. Thus, the first phase of ventricular systole is a period lasting about $1/20$ of a second, during which the pressure in the ventricle is rapidly increasing, but the volume of the ventricle remains constant. This is known as the *isometric contraction phase*. It is followed by a period, the *ejection phase*, during which the pressure in the left ventricle exceeds aortic pressure, and blood is being forced into the aorta.

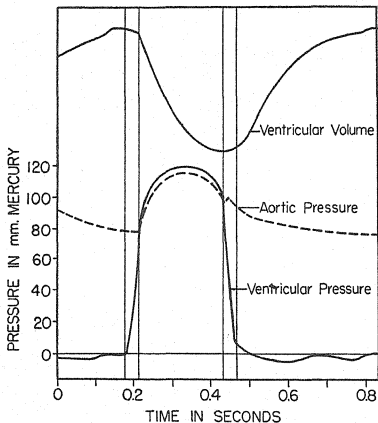


Figure 20-1. Changes in ventricular volume, left ventricular pressure, and aortic pressure during a cardiac cycle.

As the ventricle begins to relax, there is a phase of falling tension, or *isometric relaxation* period, during which the pressure in the left ventricle is less than the aortic pressure, but greater than the auricular pressure. Again, during this period, both the auriculoventricular and the aortic valves are closed and there is no change in the volume of the ventricle. When the ventricular pressure drops to below the level of the auricular pressure, the latter having built up slightly during the time that blood could not flow into the ventricle, there is a rapid influx of blood into the ventricle and then slower filling with a negligible rise in pressure until the next auricular contraction.

Ventricular volume curve. In the laboratory, information concerning ventricular volume can be obtained by the simple device illustrated in Figure 20-2. A rubber diaphragm is placed over the thistle-tube-like glass container, known as a cardiometer or cardiac oncometer, and a cut is made in the diaphragm, so that the diaphragm can be forced up to fit snugly around the auriculoventricular groove. The oncometer is connected, by means of rubber tubing, with a recording device known as a tambour. This consists of a tube connected to a metal cup covered with a rubber diaphragm and having a lever placed so that it moves up and

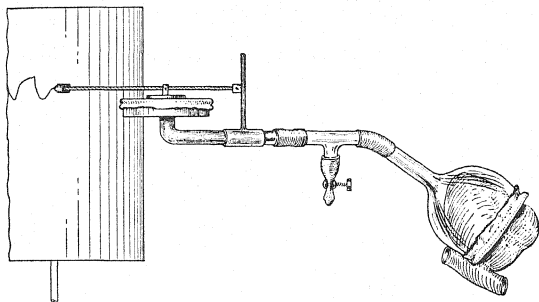


Figure 20-2. Setup for direct continuous recording of ventricular volume.

(From Youmans' *Basic Medical Physiology*.)

down with the diaphragm. Thus, the ventricles are contained in a closed space; as they fill, air is displaced into the tambour and as they contract air moves out of the tambour. The corresponding excursions of the lever are recorded by the use of a kymograph. If the drum is revolving rapidly, a curve similar to the ventricular volume tracing in Figure 20-1 is obtained. The ventricular volume record shows, consecutively, a period of rapid ejection and a period of slower ejection during systole and a period of rapid filling and then slow filling during diastole. If one is interested in the changes in diastolic and systolic ventricular size and the extent of the excursion, or stroke volume, rather than the shape of the curve produced by each heart beat, the drum is made to move slowly, and a record as shown in Figure 20-4 is obtained.

Ventricular Volume and Strength of Contraction

In 1912 to 1914 Starling and his associates used a "heart-lung preparation" to evaluate the direct responses of the heart to changes in the venous pressure or in the resistance to outflow through the aorta. In the

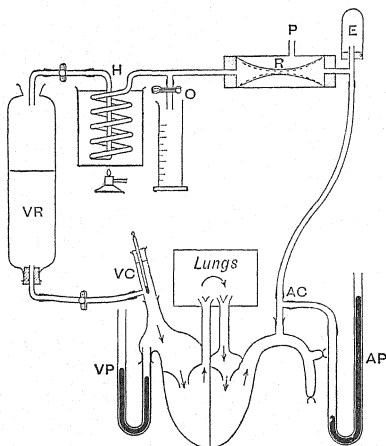


Figure 20-3. Diagram of heart-lung apparatus.

AC, arterial cannula; AP, arterial pressure; E, air chamber to provide elasticity; P, connection with pressure bottle which determines height of arterial pressure; R, resistance which is altered with changes in pressure from P; O, outlet for directly determining output during any desired interval; H, heating apparatus; VR, venous reservoir; VC, venous cannula; VP, venous pressure. (Reproduced by permission from Halliburton and MacDowall, *Handbook of Physiology*. Copyright, 1930, by The Blakiston Co.)

heart-lung preparation, a cannula is introduced into one of the great veins emptying into the right auricle and the other vein which drains into this chamber is ligated. The aorta is cannulated and the blood is passed through a device which controls the resistance to outflow from the

left ventricle. The right ventricle continues to pump blood through the lungs, which are ventilated artificially to maintain constant oxygen tension and carbon dioxide tension in the blood. The nerves to the heart are sectioned, since the purpose of the experiments utilizing this preparation is to evaluate the response of the heart itself in the absence of any reflex effects. Finally, the temperature of the blood must be kept constant, since changes in temperature cause changes in rate and strength of the heart beat, and an anticoagulant is added to the blood to prevent clotting. The setup is illustrated in Figure 20-3.

Effects of changes in venous pressure. In the heart-lung preparation, the blood is allowed to flow into the right auricle from a reservoir which can be placed at any desired height above the level of the auricle. The pressure available for production of auricular filling is expressed as the height, in centimeters of blood (which is only negligibly different from pressure in centimeters of water), from the level of the atrium to the level of the blood in the reservoir.

The experiment on effects of venous pressure consists simply of recording ventricular volume and heart rate during a period when the reservoir is at a certain level and then suddenly elevating the reservoir to a level of, for example, ten centimeters above the "control" level. When this is done, a record such as that illustrated in Figure 20-4 is obtained. It may be seen that the diastolic volume of the ventricles increases markedly, since more blood is fed in at the higher venous pressure, and the excursion of the lever, which is proportional to stroke volume, increases. In other words, systolic volume is not increased as much as diastolic volume. Thus, it is apparent that an increase in the diastolic volume of the ventricles, causing an increased length of the cardiac muscle fibers, elicits an increased strength of contraction, so that more blood is expelled per stroke. It also may be observed that the heart rate does not change. Since the amount of blood pumped by the heart per minute is the product of the heart rate and the stroke volume, and since the latter is increased, while the former is maintained, the cardiac output is increased in direct proportion to the increase in stroke volume. Stated in more general terms, the heart, in the absence of its nerve supply, is capable of responding to increased venous pressure, and hence increased filling, by an increase in output. This change serves to prevent blood from accumulating in the great veins; or, conversely, if for any reason blood tends to accumulate in the great veins, the heart responds with an increased output to transfer the blood on into the arteries. The direct response of the heart muscle to

an increase in venous pressure is supplemented by reflex influences when the nerves to the heart are intact.

If the venous pressure is increased in several steps, it may be observed that each rise is accompanied by a corresponding enlargement, or dilata

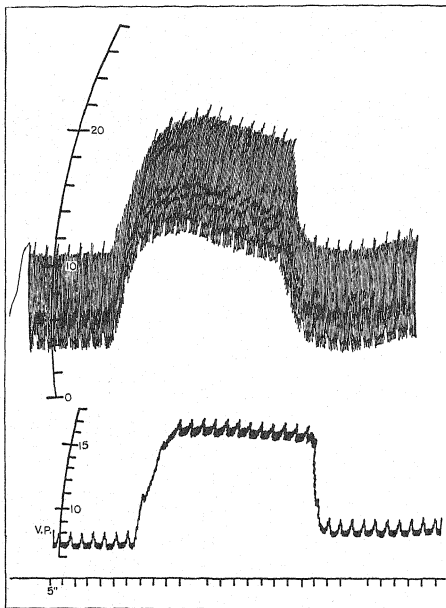


Figure 20-4. Effect of increase in venous pressure on the output of the heart.

The upper tracing is a ventricular volume record and the lower tracing is a record of venous pressure in the heart-lung preparation. The venous pressure was increased by raising the level of the venous reservoir. This resulted in an increased filling of the ventricles during diastole and an increased amount of blood pumped per stroke. Heart rate remained unchanged. Cardiac output increased in proportion to the increase in stroke volume. (Reproduced by permission from Halliburton and MacDowall, *Handbook of Physiology*. Copyright, 1930, by The Blakiston Co.)

tion, of the ventricle, and the increased length and tension in the cardiac muscle fibers elicit a stronger ventricular contraction. However, there is a limit to the increase in stroke volume that can be attained through increase in venous pressure. Eventually, as the filling pressure is elevated, the ventricle becomes dilated to the point where stroke volume, and hence cardiac output also, begin to show a decrease with further increases in pressure. The relation of cardiac output to venous pressure is shown

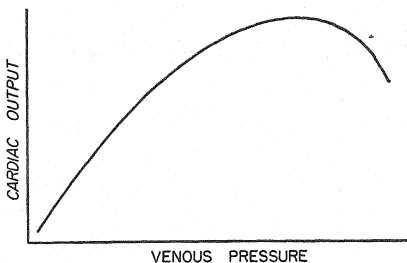


Figure 20-5. Graph of relation of cardiac output to venous pressure.

This illustrates that as the venous pressure is increased, shown toward the right on the horizontal axis, the cardiac output is increased until a certain critical venous pressure level is reached, beyond which a decrease in cardiac output occurs. No actual values are given; these differ from one heart to another or for the same heart under different experimental conditions. Curves like this are obtained from heart-lung preparations.

graphically in Figure 20-5. Specific values for pressure and output are not shown, since these vary with the size of the heart and with the conditions in each experiment.

In the normal human subject, the venous pressure levels are within a range such that any increase in venous pressure is accompanied by an increased cardiac output (unless the rise in pressure is occurring secondary to reflex inhibition of the heart itself). In patients with chronic congestive heart failure, the venous pressure may become elevated to the point that the high pressure is contributing to overdistention of the heart. Under such circumstances, withdrawal of blood may cause an increase in cardiac output.

Effects of changes in arterial pressure. The arterial pressure in the heart-lung preparation is kept constant by means of a valve (R in Figure 20-3) which will allow the blood to pass through only when a specific pressure is exceeded. Tube P is connected with a pressure source; thus, one may suddenly set the resistance at a higher level, at the same time keeping the venous pressure reservoir level (V R) constant. When this is done, it is observed that diastolic ventricular size increases for a few beats and then an equilibrium is established at which diastolic and systolic ventricular volume are increased equally; or, in other words, the stroke volume is found to be the same as before the increase in arterial

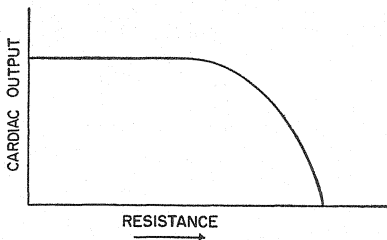


Figure 20-6. Diagrammatic representation of effect on cardiac output of increased resistance in the arterial tree.

resistance and pressure. Again, as in the experiments on effects of changes in venous pressure, the heart rate does not show a significant change; therefore, cardiac output is maintained at the level seen before the increase in resistance to outflow. Thus, the properties of the heart muscle itself are such as to maintain a constant output despite wide changes in resistance in the arterial tree. The resistance to flow may be increased stepwise until eventually the force of the cardiac contraction will not be sufficient to overcome it. When such a level is reached, cardiac output, as shown in Figure 20-6, will not be maintained.

The relationship between the length of cardiac muscle fibers and the strength of their contraction which has just been described is commonly known as Starling's law or the law of the heart. The responses obviously are such as to keep the venous pressure down and to keep up the flow of blood through the arterial tree.

Reflex Effects from Changes in Venous Pressure

The direct responses of the heart to changes in venous pressure and arterial pressure, as described above, can be studied only when the nerves to the heart are sectioned. When the nerves are intact, reflex effects upon the rate and strength of the heart beat are elicited. These reflex responses are of two types: those elicited by changes in venous pressure and those which are brought into activity by changes in pressure in the systemic arterial tree.

Whenever the blood volume is increased quickly by transfusion, the heart rate accelerates. This is the Bainbridge phenomenon. Although there are conflicting interpretations, it appears that receptors located in the walls of the great veins near their junction with the right auricle, and in the auricular wall itself, are stimulated by an increase in pressure in these structures. Impulses initiated in these receptors are carried by afferent fibers in the vagus nerve up to the medulla oblongata where they make connections with neurons that compose the cardioaccelerator and cardioinhibitory "centers." These centers, in turn, make connections with neurons which give rise to the preganglionic fibers of the vagal and the sympathetic pathways to the heart. The efferent pathways are illustrated in Figure 19-13. The preganglionic vagal fibers innervate intrinsic neurons in the vicinity of the sinoauricular and auriculoventricular nodes. The preganglionic sympathetic fibers form synapses with cell bodies in the superior, middle, and inferior cervical ganglia and in the upper thoracic ganglia, and postganglionic fibers innervate the conducting system of the heart and the cardiac muscle.

The central connections of the afferent fibers which are concerned with the Bainbridge reflex are such as to cause a decrease in the number of impulses conducted to the heart by the vagus nerves and an increase in the activity in the sympathetic nerves to the heart. Thus, a reciprocal influence on neurons in the central nervous system, similar to that described in the discussion of the flexor reflex, is involved: the braking action of the vagus nerves is decreased and the accelerator action of the sympathetics is increased. The result is an increase in heart rate and an increased strength of contraction. It may be seen readily that the Bainbridge reflex promotes an increase in cardiac output as does the response of the heart muscle to increased filling pressure.

The possibility has been suggested that the Bainbridge phenomenon

may be related to increase in pressure elsewhere than in the great veins and right atrium, for example, in other cardiac chambers or in the pulmonary vascular bed.

A rise in venous pressure can be produced in man by relatively rapid intravenous injection of blood or other fluids, and when this is done, there is an increased cardiac output for a brief period until the fluid has become distributed throughout the cardiovascular system so that no considerable rise in pressure occurs in any portion of the system.

Reflex Effects from Changes in Arterial Pressure

In the discussion of Starling's law, it was emphasized that the *direct* response of the heart muscle is such that cardiac output is maintained despite alterations in pressure and resistance in the arterial tree, and it was explained that the advantage of such a mechanism is to insure adequate flow of blood in the presence of an elevated resistance to flow. A *reflex* mechanism serves to influence the rate and strength of the heart beat when there are sudden changes in arterial pressure, and this mechanism has just the opposite effect from that related to Starling's law; it promotes a *change* in cardiac output in response to changes in arterial pressure, and the alterations in output are such as to counteract or buffer the change in arterial pressure.

The receptors concerned with reflex influences on heart rate during changes in arterial blood pressure are confined to a few localized areas, the arch of the aorta and the two carotid sinuses. The carotid sinus is a small bulbous dilatation of the internal carotid artery just above the point where the common carotid artery divides into the external and internal branches. The afferent fibers which innervate the pressoreceptors of the carotid sinuses and aortic arch are contained in the glossopharyngeal (IXth cranial) and vagus (Xth) nerves respectively. The pathways are illustrated in Figure 20-7.

A number of researchers have isolated the bifurcation of the common carotid from the remainder of the circulation in experimental animals by tying ligatures around the common carotid, external carotid, internal carotid, and one or two smaller branches in this region and have controlled the pressure within the carotid sinus. The circulation to the brain is maintained adequately through the other arteries which connect with the circle of Willis at the base of the brain. When the nerve fibers passing

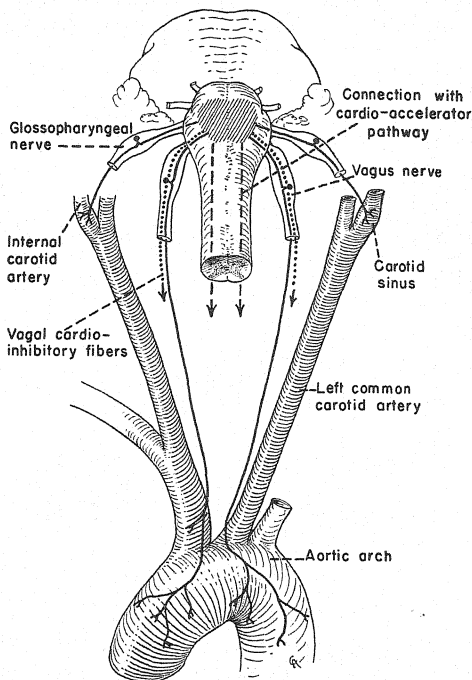


Figure 20-7. Diagram of pathways for reflex influences on heart rate elicited by changes in arterial blood pressure.

Nerve fibers shown in solid lines are afferent fibers which innervate the pressoreceptors in the aortic arch and carotid sinuses, and which connect in the medulla with the cardioinhibitory and cardioaccelerator centers. Efferent fibers from the cardioinhibitory center (dotted lines) are found in the vagus nerve; fibers from the cardioaccelerator center (broken lines) descend in the spinal cord to connect in the upper thoracic part of the spinal cord with the preganglionic neurons of the sympathetic system. For illustration of the remainder of the sympathetic pathway to the heart see Figures 9-2 and 19-13. (From Youmans' *Basic Medical Physiology*.)

from the carotid sinus to the medulla are left intact and one produces a sudden rise in pressure in the isolated carotid sinus, it is observed, as illustrated in Figure 20-9, that the heart rate and blood pressure immediately decrease and also breathing is inhibited briefly. However, even though the pressure in the sinus still is maintained, adaptation occurs relatively rapidly; heart rate and blood pressure tend to return to the levels seen before the pressure was increased, and breathing is resumed. As evidence that adaptation in this case is, in part, the phenomenon already described

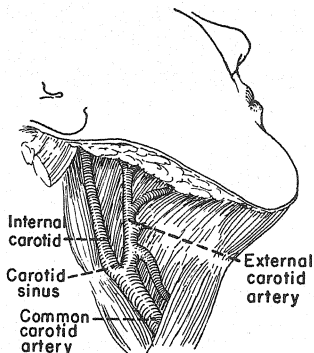


Figure 20-8. Location of the carotid sinus.

as occurring in receptors in general (page 111), one may record the frequency of passage of impulses in the carotid sinus nerve, and it is found that a burst of impulses is produced immediately at the time of increase in carotid sinus pressure and that the frequency rapidly decreases as the pressure is maintained. However, under physiological conditions, there is a pulsation in the carotid sinus with each heart beat, and a burst of impulses is set up during each ventricular systole. When the impulses from the carotid sinuses reach the medulla, they influence the same centers that are affected by afferent impulses concerned with the Bainbridge reflex, but their effects on these centers are opposite to the effects of impulses arriving from the right auricle; the impulses from the carotid sinuses cause decreased activity of the cardioaccelerator center and increased activity of the cardioinhibitory center. The influences from

a rise in pressure in the aortic arch apparently are similar in every respect to those from the carotid sinuses. These pressure-sensitive areas

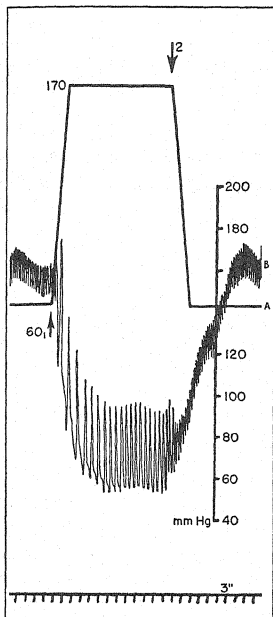


Figure 20-9. Reflex effects on heart rate and blood pressure elicited by elevating the pressure in a perfused carotid sinus.

A, pressure in carotid sinus. B, record of arterial blood pressure by means of a mercury manometer. Lowermost line shows time in 3-second intervals. (Reproduced by permission from Heymans, *Introduction to the Regulation of Blood Pressure and Heart Rate*. Copyright, 1950, by Charles C Thomas Publishers.)

through reflexes are exerting a constant restraining influence on heart rate and, as will be described later, they also cause an inhibition of the tonus of smooth muscle in the arterioles. The carotid sinus and aortic arch reflexes counteract a rise in arterial blood pressure by producing a decrease in heart rate and a decrease in resistance to flow through the arterioles. During a fall in blood pressure, their action is suspended and this releases the heart and arterioles from inhibitory influences, so that any decrease in pressure also is buffered. The buffer reflexes are protective in that, on the one hand, they help to maintain an adequate head of pressure in the arterial tree and, on the other hand, they help to prevent a sudden excessive increase in pressure which might rupture an artery.

The role of the buffer nerves also can be demonstrated either by direct stimulation or by observing the effects of sectioning the nerves. If the afferent nerve from either the aortic arch or carotid sinus is sectioned and the central end is stimulated, a decrease in heart rate and blood pressure is produced. This type of response is the basis for the name, *depressor nerve*. If the four depressor nerves are sectioned, one after the other, typically, there is an increase in heart rate and blood pressure produced

by cutting each nerve, and when all four buffer nerves are sectioned, a condition known as *experimental neurogenic hypertension* is produced. The blood pressure and heart rate are greatly increased.

Reflex liberation of epinephrine. At the same time that a severe decrease in blood pressure causes acceleration of the heart through the buffer reflexes, liberation of epinephrine from the adrenal medulla is elicited on a reflex basis. When the epinephrine reaches the heart, it produces an effect similar to that produced by increased activity of the adrenergic nerves to the heart; the rate and the strength of contraction are increased. This is one of numerous examples of the supplementary activity of the adrenal medulla and the sympathetic nervous system. The sympathoadrenal system is activated also in fright, rage, asphyxia, and during hemorrhage.

Heart Sounds

During the cardiac cycle, vibrations are set up by the contraction of the heart muscle, by the closure of the heart valves, and by the flow of blood at high velocity. These vibrations are transmitted to the surface of the body and can be heard by means of a stethoscope. The vibrations of the body are transmitted to the column of air extending from the bell of the stethoscope through the rubber tubing to the ear.

During each beat of the normal heart, two sounds regularly are heard. The *first sound* begins at approximately the beginning of ventricular systole and continues through the isometric contraction phase into the ejection phase. The *second sound* occurs during the early part of the isometric relaxation phase. In some normal subjects, a "physiologic third sound" is heard immediately after the second sound, and sometimes a very weak sound can be heard, in the normal subject, beginning just before and fusing with the first sound.

It is generally accepted that the first sound is a composite of vibrations originating from three sources as follows:

- (1). Vibration of the walls of the contracting ventricles.
- (2). Vibrations set up by the sudden closure of the A-V valves.
- (3). Vibrations of the aorta and pulmonary artery.

Normally, auricular systole contributes little or nothing to the first sound, but produces a prominent "presystolic" sound if the orifice of the mitral valve is reduced in size as a result of scarring. The second sound is produced by the vibrations set up by the closure of the aortic and pulmonic

valves at the time when intraventricular pressure falls below the pressure in the respective arteries. The closure of these valves, as previously described, marks the beginning of the isometric relaxation period. The physiologic third sound, when present, occurs early in diastole at the end of the period of rapid ventricular filling; it is attributed to vibrations of the ventricular walls produced by the sudden influx of blood from the auricles.

The vibrations of the thoracic wall produced by the heart's action can be amplified and transmitted to recording devices, so that a graphic record is obtained. Such a record, known as a *phonocardiogram* (Figure 20-10), shows the frequency and relative amplitude of the vibrations. It

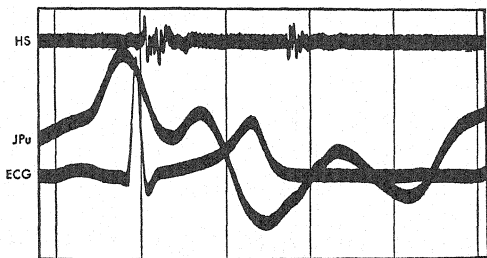


Figure 20-10. Simultaneously recorded heart sounds (HS), jugular pulse (JPu), and electrocardiogram (ECG) in a normal subject.

(Reproduced by permission from Groedel, *The Venous Pulse and Its Graphic Recording*. Copyright, 1946, by Brooklyn Medical Press.)

shows all vibrations produced; some of these may be of a frequency or amplitude so low that they are inaudible. Frequently, the electrocardiogram is recorded simultaneously with the phonocardiogram in order to establish unequivocally the phase of the cardiac cycle at which each sound occurs.

The relative loudness of the first and second heart sounds varies according to the position on the chest where the bell of the stethoscope is placed. Areas are established for each of the four heart valves. In general, at the aortic area, sounds originating from the aortic valves are heard best; at the mitral area, sounds originating from the mitral valve are heard best, etc.

Murmurs. When blood is forced at a relatively high velocity through an orifice into a vessel or chamber of somewhat larger cross sectional area, turbulence is produced, and the vibrations induced by this turbulence are heard as murmurs. Most commonly, heart murmurs are related to failure of a valve to open completely (*stenosis*) or failure to close completely (regurgitation or *insufficiency*). Also, in conditions in which the cardiac output is considerably increased, particularly if the viscosity of the blood is low, as in anemia, turbulence may occur and murmurs are heard in the absence of any abnormality of the cardiac valves.

Chapter 21

CONTROL OF ARTERIOLAR TONUS

Relation of Arteriolar Tonus to Pressure and Flow

The mean pressure at any given point in the systemic arterial tree represents a balance between the rate at which the left ventricle pumps blood into the aorta and the rate at which the arterioles permit the blood to flow out into the capillary beds. Changes in mean arterial pressure are produced as a result of a change in either the cardiac output or in the resistance to outflow from the arteries. The resistance to flow of blood in the systemic circuit is referred to as the *peripheral resistance*. As explained previously, little resistance is encountered in the larger vessels; the major fraction of the resistance is found in the arterioles, and it is here that the pressure falls off rapidly. Wide and rapid changes in peripheral resistance are possible, since the diameter of the arteriolar lumen can vary with changes in tonus of the smooth muscle in the arteriolar wall. Changes in arteriolar tonus can occur either as a result of the direct influences on the smooth muscle of local chemical changes or as a result of impulses reaching the smooth muscle by the nerve supply.

The resistance encountered in a vascular bed can be determined by making use of the relationship:

$$\text{Flow} = \frac{\text{Pressure}}{\text{Resistance}}$$

This formula indicates that the amount of flow which will be produced through a system of tubes is *directly proportional to the pressure* being exerted and *inversely proportional to the total resistance* encountered. For example, flow could be doubled either by doubling the pressure without altering the caliber of any of the tubes, or, on the other hand, by increasing the caliber of the tubes so that the resistance is halved while keeping the pressure constant. It is possible to perfuse an artery, for

example that supplying a rabbit's ear, with fluid fed in under a constant head of pressure from a reservoir and to measure the volume of outflow from the vein for a given period. One may then stimulate the nerves which supply the smooth muscle in the blood vessels of the rabbit's ear, and observe that the outflow diminishes markedly. It can be deduced that

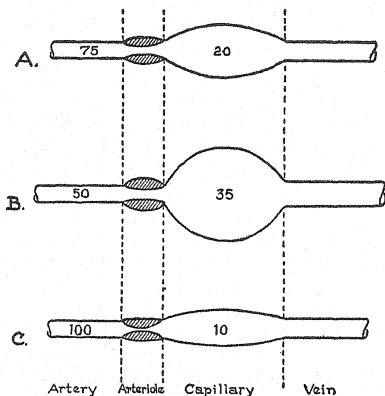


Figure 21-1. Diagram showing effects of alterations in arteriolar tonus upon pressure and volume in the capillaries.

A, "control." B, decreased arteriolar tonus: the arterial pressure decreases, pressure and volume in the capillary bed increase. C, increased arteriolar tonus: effects are opposite to those seen in B. (Reproduced by permission from Youmans and Huckins, *Hemodynamics in Failure of the Circulation*. Copyright, 1951, by Charles C Thomas Publishers.)

stimulation of the nerves has caused an increased resistance to flow, and this is known to be due mainly to the action upon smooth muscle in the arteriolar walls.

Another method for detecting changes in resistance in a vascular bed is to pump fluid through the vessels at a constant rate and to measure any changes in pressure which must develop in the perfusion system to keep the flow constant; in this case, if resistance increases, then pressure increases proportionately as flow is maintained.

The *volume* of an organ which is being perfused with blood under a

constant head of pressure changes with changes in arteriolar tonus. The basis for this is illustrated in the schema in Figure 21-1. Note that the pressure beyond the resistance increases as the resistance decreases when the arterioles relax. The tube beyond the resistance corresponds to the thin-walled capillary. When the caliber of the arteriole changes, this is reflected in a change in pressure in the capillary and this in turn is associated with a change in volume of the capillary. If a substance which produces vasodilatation is injected into the perfusion system when the flow is being kept constant by means of a suitable pump, one observes that the pressure required to maintain flow is decreased and at the same time the volume of the organ increases. Opposite effects are produced during vasoconstriction.

The changes in the caliber of arterioles produced secondary to increases or decreases in the tonus of the smooth muscle in the arteriolar wall are referred to as active vasoconstriction or active vasodilatation respectively. If the caliber of the arteriole is changed simply by corresponding changes in pressure within the lumen, the alteration is called passive vasoconstriction or passive vasodilatation, as the case may be. It is possible for the smooth muscle of the arteriolar wall to be brought under excitatory influences and at the same time for the pressure in the lumen to be considerably increased as a consequence of transfer of blood into this vascular bed from other portions of the circulatory system and, under these circumstances, the caliber of the arteriole may be increased despite the increased tonus of the arteriolar smooth muscle.

Neural Influences upon Arteriolar Tonus

The neural mechanisms. The smooth muscle of the arterioles is controlled by mechanisms which, in their general makeup, resemble those which control the heart rate. In this case, also, there is a center in the medulla oblongata which has the function of integrating the neural influences upon arteriolar tonus. This center is known as the *vasomotor center*. It consists of reciprocally acting parts, the *vasoconstrictor center* and the *vasodilator center*, but the former is of considerably greater importance than the latter. Cell bodies in the vasomotor center give rise to axons which make connections with the preganglionic neurons of the two divisions of the autonomic system which, in turn, innervate the smooth muscle of the arterioles. The vasoconstrictor center makes connections mainly with the thoracolumbar part of the autonomic system and the vasocon-

strictor nerves are, for the most part, adrenergic. The vasodilator center connects primarily with the craniosacral outflow and the vasodilator nerves are predominantly cholinergic. However, there are exceptions to these generalizations.

If epinephrine is injected into an experimental animal in relatively large doses, it produces, in addition to the effects on the heart, a severe constriction of the arterioles in the skin and in most of the abdominal organs. At the same time, it produces dilatation in the arterioles in skeletal muscle and possibly in the heart muscle, but the overall effect is an increase in the peripheral resistance. This indicates that the vasoconstrictor effect is quantitatively more important. In doses which produce blood levels of epinephrine within the physiological range, there may be little or no increase in peripheral resistance and the main effect is redistribution of blood flow. When choline derivatives are injected intravenously, they produce an effect on the arterioles which is opposite to that of epinephrine. Blood pressure is reduced and the volume of the abdominal organs is increased.

Reflex effects from the pressoreceptors. Changes in tonic activity of the vasoconstrictor center are produced when there are changes in the arterial blood pressure. A sudden rise in pressure in the carotid sinuses or aortic arch stimulates the pressoreceptors, and impulses are conducted to the vasoconstrictor center by the IXth and Xth cranial nerves. The center is inhibited so that fewer impulses are conducted over the efferent vasoconstrictor pathways to the arteriolar smooth muscle. The cardiac inhibition produced simultaneously already has been described (page 240). Thus, a rise in arterial pressure is buffered both by a decreased resistance to outflow from the arterial tree and a decreased input. A sudden fall in arterial pressure has the reverse effects; the arterioles are constricted reflexly and the heart rate is accelerated. If the fall in blood pressure is severe, epinephrine is liberated from the adrenal glands.

In experimental animals, the role of the buffer nerves in influencing vasoconstrictor tonus can be demonstrated either by sectioning or by stimulating the nerves. For example, if the carotid sinus nerves are sectioned, the blood pressure rises and at the same time the volume of the intestine, kidney, spleen, etc., decreases. If the central end of the sectioned carotid sinus nerve is stimulated, a decrease in blood pressure and an increase in volume of these organs results. The effects on heart rate are not quite so predictable, since two influences are working in opposite directions and either influence may predominate. Impulses

passing up the carotid sinus nerve which is being stimulated would tend to cause a decrease in heart rate, but the fall in blood pressure in the other carotid sinus and in the aortic arch incident to the vasodilator effects, tends to cause cardiac acceleration.

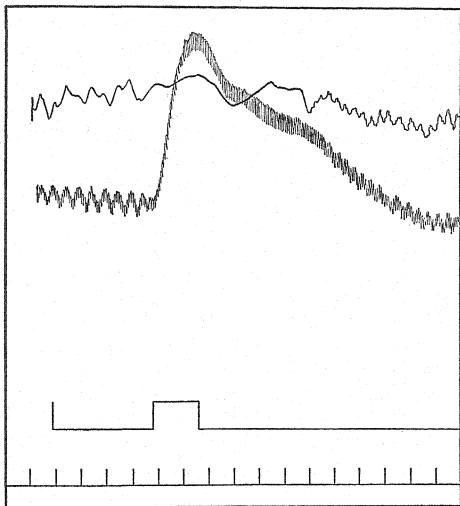


Figure 21-2. Rise in blood pressure secondary to vasoconstriction produced by stimulating the central end of the sectioned vagus nerve in a dog under morphine-ether anesthesia.

From above downward, tracings show volume of a segment of intestine, pressure from the femoral artery by means of a mercury manometer, time of stimulation of the vagus, and time in 5-second intervals.

In dogs, the afferent fibers coming from the aortic arch are contained in the vagosympathetic trunk, but in rabbits there are separate aortic (*depressor*) nerves which are composed entirely of afferent fibers. Stimulation of the central end of the aortic nerves causes effects similar to those produced by stimulation of the carotid sinus nerves or by distention of the carotid sinus.

Section of all four nerves innervating the pressoreceptors results in a chronically increased peripheral resistance as well as an elevated heart rate and cardiac output. Consequently, the arterial blood pressure is markedly elevated.

Reflex effects from the chemoreceptors. Since a major function of the circulatory system is the transport of oxygen to the tissues, it is not surprising that the body is equipped with mechanisms which serve to increase the rate of blood flow when the oxygen tension in the blood is inadequate. Small bodies which are located in the bifurcation of the common carotid artery near the carotid sinuses and around the aortic arch receive a rich blood supply by short branches from the adjacent large arteries and are innervated by the IXth and Xth cranial nerves. The carotid and aortic bodies (Figure 26-5, page 303) contain receptors that are particularly sensitive to a lowering of the oxygen tension of the blood; in the presence of this change, the number of impulses conducted by the afferent nerves is increased. The influences of these impulses in the medullary center can be demonstrated by isolating a carotid body from its normal circulation and perfusing it with blood at controlled oxygen tensions. When the oxygen tension of the perfused blood is lowered somewhat below the normal range, breathing is stimulated (page 302), blood pressure increases, and heart rate decreases. This result is different from that obtained when the intact subject breathes a gas containing less than the normal oxygen tension in that in the latter case an increase in heart rate is seen along with the stimulation of breathing and increased blood pressure.

It appears that the chemoreceptors of the aortic and carotid bodies constitute the body's first line of defense against a decrease in oxygen tension in the inspired air. The number of impulses being initiated in these receptors when one is breathing atmospheric air at sea level is negligible; but, as one ascends to higher altitudes, the oxygen tension in the inspired air progressively decreases and, consequently, there is a decrease in the oxygen tension in the alveoli of the lungs and in the systemic arterial blood which reaches the chemoreceptors. The increase in blood pressure and in breathing which occurs at altitude is attributable to reflexes elicited from the carotid and aortic bodies. The increase in heart rate, apparently, is produced by some other mechanism.

Responses of the chemoreceptors to H^+ concentration and CO_2 tension. The chemoreceptors also respond to changes in H^+ concentration (cH) and CO_2 tension. An increase in cH or in CO_2 tension of blood being

perfused through a carotid body will elicit an increase in blood pressure and respiration; however, the changes necessary to produce these responses are considerable and would not occur in the normal individual, since the centers in the medulla which are very sensitive to changes in cH and CO_2 tension would act to prevent the development of such severe alterations. In disease, on the other hand, and in persons under the influence of drugs which depress breathing, reflexes from the chemoreceptors elicited by an increase in CO_2 and cH may be important, especially in the maintenance of breathing (page 302).

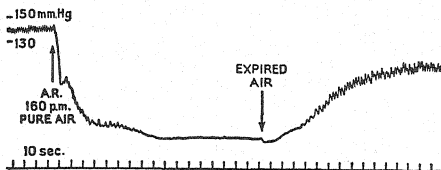


Figure 21-3. Fall in blood pressure produced by hyperventilation with air and counteracted by hyperventilation with expired air (rich in CO_2).

A. R., artificial respiration at rate of 160 per minute. At the second arrow, ventilation rate was unchanged, but expired air was used instead of atmospheric air. (By permission from Wright, after Dale and Evans, *J. Physiol.*, 56:127, 1922.)

Effects from the vasoconstrictor center. The vasoconstrictor center itself is particularly sensitive to changes in carbon dioxide tension. The wide changes in blood pressure produced by hyperventilation or by breath-holding are produced largely on this basis. The effect is particularly evident in an anesthetized animal receiving artificial respiration, in which case the level of the blood pressure can be determined by the level of the ventilation. As the ventilation is increased, the CO_2 tension of the blood decreases and there is a decreased activity of the vasoconstrictor center and, consequently, a fall in blood pressure.

A change in the CO_2 tension in the vasoconstrictor center can be produced by impairment of the blood flow through this part of the brain. The neurons are continually producing CO_2 and if this is not carried away as fast as under normal conditions, the level in the cells will be increased. The effects on blood pressure, during an increased intracranial pressure, may be explained by this mechanism. Since the cranial cavity is a rigid closed space, when there is an increased volume of the contents,

for example an intracranial hemorrhage, there is an increase in pressure. The increase in pressure against the walls of the capillaries in the brain tends to collapse them and thus obstructs the blood flow. When the blood flow through the vasoconstrictor center is decreased, the carbon dioxide tension is increased, and this causes an increased activity of the vaso-

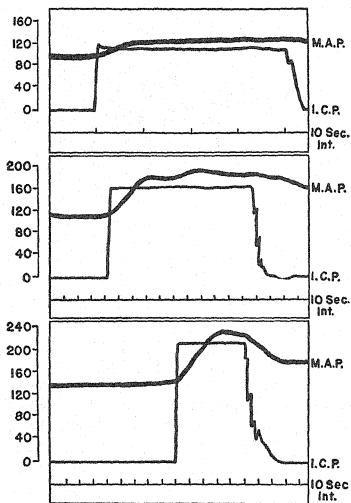


Figure 21-4. Effect of increased intracranial pressure (I.C.P.) on mean arterial blood pressure (M.A.P.).

Pressure for both manometers is shown on left in millimeters of mercury. (From Youmans' *Basic Medical Physiology*.)

constrictor nerves, which in turn increases the arteriolar tonus in the systemic circuit. Arterial blood pressure then is elevated to a level which is just sufficient to restore blood flow through the centers.

A rise in intracranial pressure can be produced artificially in the experimental animal. In the experiment illustrated in Figure 21-4, three different pressures were established and removed consecutively in an anesthetized

dog having the buffer nerves sectioned. In each case, the intracranial pressure was increased to a level above the mean arterial blood pressure and then the arterial blood pressure rose to a level above the intracranial pressure. Thus, cerebral circulation was restored, in spite of the elevated intracranial pressure. In animals having the buffer nerves intact, similar changes in arterial pressure occur in response to increased intracranial pressure, but the heart rate decreases.

The vasoconstrictor center also is influenced by nerve impulses reaching it from higher centers in the brain. This is especially important in the production of alterations in the circulation in the skin which occurs as a part of the heat regulating process (page 436).

Effects of Local Chemical Changes

When the activity of a tissue increases, there is an increased rate of oxygen consumption, an increased rate of production of carbon dioxide, and accumulation of acid metabolites. Consequently, the oxygen tension in the tissue is lowered, and the carbon dioxide tension and hydrogen ion concentration increase. Each of these three changes has a direct relaxing effect on the smooth muscle in the arterioles, and the lowered resistance incident to local arteriolar relaxation allows an increase in the rate of blood flow through the active tissue if the arterial pressure is maintained.

If the pressure in the artery supplying the tissue is decreased, for example, by partial obstruction of the vessel, the decreased pressure will result in a decreased blood flow, and the same changes as those initiated by an increase in metabolism will occur. The ill effects of the obstruction are counteracted in part by a decreased resistance in the arterioles, and this helps to restore blood flow.

The mechanisms which influence arteriolar tonus have been seen to be of two main categories, local and general. The principal mechanisms which influence arteriolar tonus, generally, are the reflexes from the pressoreceptors of the carotid sinuses and aortic arch, the reflexes from the chemoreceptors elicited by a fall in oxygen tension of the blood, and, finally, the influences from changes in the vasoconstrictor center. The local influences in any one organ may be such as to counteract the change that would be produced by the reflex or central mechanisms. In this way, the special needs of individual organs or parts of the body are provided for without any interference with the general regulatory mechanisms.

Chapter 22

BLOOD PRESSURE AND BLOOD FLOW

Cardiac Output

In the normal individual, the cardiac output varies directly with changes in the total oxygen consumption of the body. The oxygen consumption under resting conditions is a measure of the *basal metabolic rate* (pages 344-346). Usually, if the basal metabolic rate is either elevated or decreased, the cardiac output correspondingly is altered. An increase in oxygen consumption to as much as twelve times the basal rate can be produced by muscular exercise, and, in this case, the cardiac output increases to 8 or 9 times the basal level through an increase in both heart rate and stroke volume. The oxygen uptake may be increased to twelve times the normal level in the presence of the ninefold increase in cardiac output, since there is also an increase in the amount of oxygen which is absorbed by the tissues from each unit of blood; consequently, the blood returning to the right side of the heart contains less oxygen than it carries under basal conditions, but, as the blood flows through the lungs, oxygen is taken up in sufficient amounts to produce a level in the arterial blood that is near the level which is found under resting conditions.

Measurement of cardiac output. In experimental animals, cardiac output can be measured by recording stroke volume and heart rate by means of an oncometer. In intact animals and in man, indirect methods must be employed. Methods for measuring cardiac output, employing a principle described by Fick, have been used widely. In the methods based on the *Fick principle*, two things are determined: (1) the total amount of a substance, for example, oxygen, which is taken out of the blood as it flows through the systemic circuit during a given period of time; and (2) the amount of the substance removed from each 100 ml. of blood. To determine how much oxygen is removed in the tissues per 100 ml. of blood, one determines the oxygen content of the arterial blood and of the mixed venous blood, and then subtracts the latter from the former. Thus, if arterial blood contains 19 volumes per cent of oxygen, and mixed

venous blood contains 14 volumes per cent, the tissues are removing 5 ml. of oxygen from each 100 ml. of blood. If the body is using 250 ml. of oxygen per minute (determined by methods described on page 12), it is apparent that 250/5, or 50 times 100 ml. of blood, would be delivering this amount of oxygen per minute. The formula is as follows:

$$\frac{\text{O}_2 \text{ consumed per minute}}{\frac{\text{volumes \% of O}_2 \text{ in arterial blood} - \text{volumes \% of O}_2 \text{ in venous blood}}{}} \times 100 = \text{cardiac output in ml. per minute}$$

Velocity and Volume of Blood Flow

Cardiac output per minute is the product of the heart rate and the average stroke volume. Average values for heart rate, stroke volume, and left ventricular output in a normal resting individual are 70, 60, and 4200 respectively. The total amount of blood which flows through all of the vessels of the systemic circuit during a given period must be equal to the amount which is pumped by the left ventricle. At the level of the aorta, all of the left ventricular output passes through a relatively small area, namely, the cross-sectional area of the aorta. As the aorta branches and rebranches, the sum of the cross-sectional area of the branches, known as *total cross-sectional area*, is greater than that of the aorta, but the total blood flow through all of the branches can only equal the flow through the aorta. As the arterial tree branches repeatedly, the total cross-sectional area steadily becomes larger, until it is largest at the capillary level where it is many times that of the aorta; nevertheless, no more blood can flow through all of the systemic capillaries per minute than enters the aorta from the left ventricle. On the venous side, the blood flows through a smaller and smaller total cross-sectional area as the veins join and the blood approaches the heart. In the pulmonary circuit, there is again a small cross-sectional area of the pulmonary artery through which all of the cardiac output must pass and a progressive increase in cross-sectional area to reach a maximum in the pulmonary capillary bed and then a reduction as the pulmonary veins are approached.

The velocity of blood flow at any given level of the cardiovascular system depends upon the cardiac output and upon the total cross-sectional area at that level. If we assume, as under basal conditions, that the cardiac output is remaining constant, then velocity at a given level is determined entirely by the total cross-sectional area at that level. This may be visualized by considering a stream that flows into a lake which overflows

into another stream. The *total* flow past any cross section of the entering stream, the lake, or the effluent stream is the same, but, since the cross section of the afferent and efferent streams is low, while that of the lake is high, the volume of flow *per unit* cross-sectional area is low in the lake and high in the streams. Velocity refers to rate of movement of the liquid, and this is directly proportional to the volume which passes a given point per unit of cross-sectional area. Velocity may be measured in two ways: (1) the time required for a particle or a unit of blood to traverse a given distance may be determined, or (2) the volume flowing past a given unit of cross-sectional area may be measured.

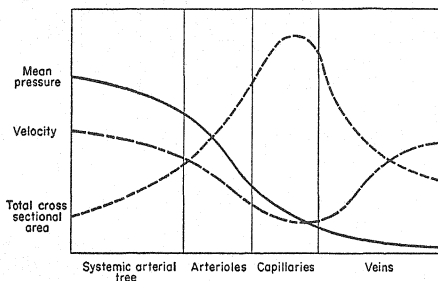


Figure 22-1. Pressure and velocity in the systemic circuit.

Since total cross-sectional area is greatest in the capillary beds, velocity of flow here is least. This is appropriate, since the functions of the circulatory system actually are performed in the capillary beds where time is required for the interchange of materials across the capillary wall between the blood and the interstitial fluid. It is also beneficial that velocity be high in the vessels which serve solely as conduits to convey the blood to and from the heart. The direction of the changes in velocity in the systemic circuit are illustrated in Figure 22-1. A curve of similar shape would illustrate velocity changes in the pulmonary circuit.

Circulation Time

The usual method used in the measurement of the time required for blood to flow from one part of the circulatory system to another is to

inject into a vessel a substance which may be detected immediately on its arrival at a certain part of the circulatory system. For example, a counter which detects radioactivity may be placed over a vein in one arm, while a harmless radioactive compound is injected into a vein of the other arm, and the radioactive particles can be detected immediately by the clicking of the counter when they arrive in the vein on the other side. Since the blood passes by the systemic veins to the heart and through the pulmonary circuit out into systemic arteries and back to a point corresponding to the site of injection on the opposite side, a *total circulation time* is measured. Other substances may be injected intravenously which produce a characteristic reaction immediately on reaching certain parts of the systemic capillary bed. Saccharin will produce a sweet taste when it reaches the capillaries of the taste buds, hence it may be used as a measure of *arm-to-tongue* time; it approximates a complete circulation time. *Arm-to-lung* time is measured by injecting a few drops of ether into a vein of the arm and having the subject state when he first smells the ether. The ether passes up the vein to the right side of the heart and out by the pulmonary arteries to the capillaries of the lungs; it diffuses into the alveoli of the lungs and is exhaled past the olfactory mucosa in the nasal passages. The total circulation time in normal subjects under resting conditions is usually between 20 and 25 seconds, while the arm-to-lung time, of which one or two seconds is utilized for movement of the ether from the alveoli to the olfactory mucosa, is about 8 seconds.

The velocity of flow and the volume of flow *past a given point* in a vessel also have been measured by a number of methods; however, an objection to most of these methods is that it is necessary to expose the vessel and place objects around the vessel wall or in the lumen.

Pressure Gradients

The mean pressure in the aorta ranges around 90 to 100 mm. of mercury in normal subjects at rest. Pressure progressively decreases along the systemic arterial tree, but does not show a sharp drop until the arterioles are reached. Here the pressure drops from about 60 to 70 mm. of mercury down to about 25 to 30 at the arteriolar end of the capillary. A further drop of some 10 mm. occurs in the capillary, and 15 mm. of mercury is taken as an average figure for the venous end of the capillary.

Since the average pressure in the right atrium is near zero (i.e., atmospheric), a decrease in pressure of only about 15 mm. is found from the capillaries along the venous system back to the atrium. The mean pressure gradient for the systemic circuit is illustrated in Figure 22-1. Since the head of pressure which is produced in the aorta by the pumping action of the heart is used up in overcoming resistance to flow, it is evident that relatively little resistance to flow is encountered except in the small vessels in the periphery of the systemic circuit.

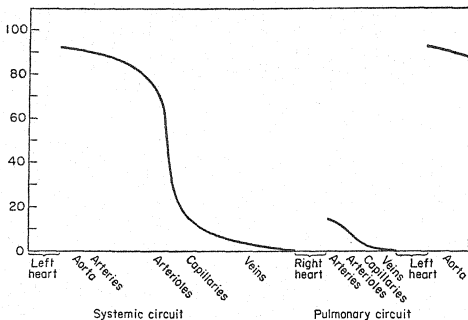


Figure 22-2. Comparison of pressure gradients in the systemic and pulmonary circuits.

In the pulmonary circuit, the mean pressure in the pulmonary artery is approximately 15 mm. of mercury. Since the same amount of blood is pumped through this circuit as is forced through the systemic circuit, it can be calculated that the total resistance in the pulmonary circuit is approximately one-sixth as great as that in the systemic circuit.

Indirect Recording of Blood Pressure

In experimental animals, arterial blood pressure commonly is recorded by the direct method which involves the introduction of a needle or cannula into the lumen of the artery and connecting this by means of tubing with a pressure-recording device. For the routine measurement of blood

pressure in the human subject, an indirect method is used. The instrument employed, the *sphygmomanometer* (*sphygmos*—pulse), consists of a rubber bag surrounded by a cloth cuff and connected by means of rubber tubing with a suitable manometer. The bag, supported by the cuff, is placed around the upper arm and air is pumped into the bag by means of a rubber bulb attached to a side arm which leads to the rubber tubing connecting the bag with the manometer. The standard procedure is to

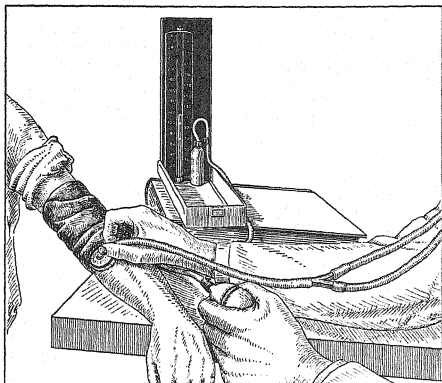


Figure 22-3. Use of sphygmomanometer to record arterial blood pressure.

(By permission from Amberson and Smith, *Outline of Physiology*. Copyright, 1939, by Williams and Wilkins.)

determine the systolic pressure first by the *palpatory* method and then to determine systolic and diastolic pressures by the *auscultatory* method.

While the patient's radial pulse is being palpated, the air is pumped rapidly into the bag until the pressure indicated by the manometer is about 30 mm. of mercury above that needed to obliterate the pulse. The pressure in the bag is transmitted to the arm and forces the artery shut and keeps it shut if the pressure in the bag exceeds the maximum pressure within the artery. Then a valve on the bulb is opened slightly to release air slowly so that the pressure falls about 2 or 3 mm. of mercury per heart beat. The systolic pressure is approximately the level at which one can

again feel the radial pulse. When the systolic pressure is observed, the bag is rapidly and completely deflated before proceeding with the auscultatory method.

Auscultatory method. The bell of a stethoscope is placed over the artery in the antecubital space just below the cuff. The pressure in the bag is again raised above the systolic level determined by palpation and the pressure is allowed to decrease slowly. No sound is heard when the pressure in the bag exceeds the systolic pressure. When the pressure in the bag drops just below the systolic level, the walls of the artery are forced open momentarily and this produces a sound. Thus, systolic pressure is the highest pressure at which one can hear a sound with each heart beat. This reading usually is a little higher than that obtained by the palpatory method. With continued slow deflation of the cuff, the sounds undergo changes and, as the diastolic pressure is approached, the sounds decrease suddenly and shortly disappear. The point of disappearance of the sounds is considered to be the best index of diastolic pressure; however, under abnormal conditions, no cessation of sounds occurs and in these instances the point of sudden decrease in the sounds is taken as the diastolic pressure. In short, sounds normally can be heard over the artery when the pressure in the cuff is somewhere between systolic and diastolic pressure, whereas if the cuff pressure is above the systolic or below the diastolic, no sounds are heard.

In normal adults at rest, the systolic pressure usually is between 110 and 140, and the diastolic pressure is between 60 and 90. The pulse pressure, namely, systolic minus diastolic, usually is 30 to 50 mm. of mercury.

High Blood Pressure

Since the pressure in the arterial tree represents a balance between the rate at which blood is being pumped into the system by the heart and the total resistance to outflow from the arterial tree, it is apparent that, with resistance to outflow remaining unchanged, an increase in cardiac output would cause an increase in arterial blood pressure; or, if the cardiac output were kept constant and resistance to outflow, as from widespread arteriolar constriction, should increase, the arterial blood pressure would increase. Elevation of both cardiac output and peripheral resistance, of course, would cause a still greater rise in arterial blood pressure than would result from either change alone. It has already been explained how

a sharp rise in blood pressure produced by a sudden increase in peripheral resistance is counteracted, through carotid sinus and aortic arch reflexes, by a decrease in heart rate and cardiac output; however, when the rise in pressure is prolonged, the pressoreceptors adapt and the heart rate tends to return to the normal range.

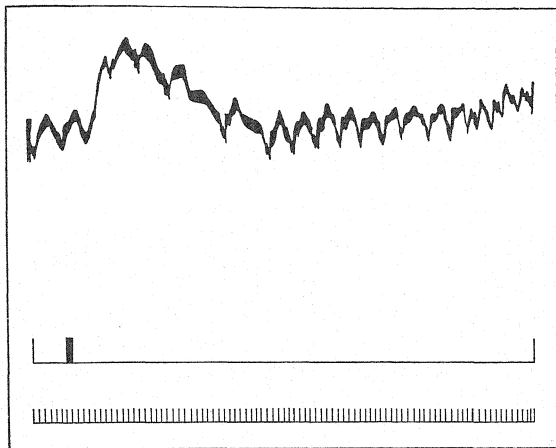


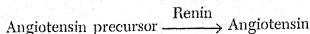
Figure 22-4. Effect of angiotensin on the arterial blood pressure of an anesthetized dog.

Time of injection of angiotensin is shown by procedure record (middle), and time in 2-second intervals is indicated by the bottom line. The procedure record also is the zero pressure line for the mercury manometer. The vagus nerves have been sectioned to eliminate the reflex cardioinhibitory response to the rise in blood pressure. Heart rate does not show on this record because the heart rate is fast and the drum speed is slow, so that the excursions due to heart beats are fused. The prominent slow waves are produced by respiration.

The most severe forms of high blood pressure are those which occur secondary to an increased peripheral resistance. Cardiac output is not increased; usually, it is normal and in later stages of the illness it may be decreased. The most common form of high blood pressure is known as *essential hypertension*. In this disease, the hypertension is due to an in-

creased resistance at the arteriolar level, but the mechanism for production of the changes in the arterioles is not known.

Renal hypertension. A type of hypertension produced by interfering with the blood supply to the kidney has been produced in experimental animals and has been shown to occur occasionally in man. This is known as *renal hypertension*. Partial occlusion of a renal artery causes the production in the corresponding kidney of a substance, probably an enzyme, known as *renin*. Renin acts upon a globulin called angiotensin precursor, which is present in normal blood, to produce angiotensin.



Angiotensin has a vasoconstrictor action, and hence causes an increase in the peripheral resistance. The heart muscle responds to the increased arterial pressure with increased strength of contraction, and this serves

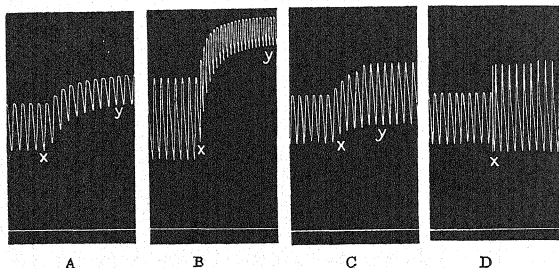


Figure 22-5. Factors affecting systolic and diastolic pressures.

A, effect of increased peripheral resistance; B, effect of increase in heart rate; C, effect of increased stroke output; D, effect of decreased elasticity of "arterial" tree. (Reproduced by permission from Wiggers, *Physiology in Health and Disease*. Copyright, 1949, by Lea and Febiger.)

to maintain a normal output despite the increased load. Renal tissue which has an adequate circulation produces an enzyme, angiotensinase, which inactivates angiotensin; therefore, impairment of renal circulation unilaterally is less likely to cause hypertension than when both kidneys have their blood supply impaired.

Factors determining pulse pressure. Although the *mean* arterial blood pressure is determined by the cardiac output and the peripheral resist-

ance, the *pulse pressure* is related to heart rate, stroke volume, and elasticity of the arterial tree as well as to the peripheral resistance. An increase in heart rate in the presence of no change in stroke volume or in the caliber of the arterioles causes a rise in mean arterial pressure and a decrease in pulse pressure, since the diastolic pressure under these conditions is elevated by a greater amount than the systolic pressure. Any change in stroke volume, rate and peripheral resistance remaining constant, is associated with a corresponding change in pulse pressure. A decrease in arterial elasticity, or arteriosclerosis, is associated with a rise in systolic pressure and a fall in diastolic, hence a marked increase in pulse pressure, with little or no change in mean pressure. This type of alteration occurs to some extent as a normal part of the aging process.

Low Blood Pressure

There are few conditions that cause a chronically low arterial blood pressure. A severe lowering of the blood pressure is more apt to be temporary than sustained. Usually, it is caused either by decreased action of the heart, or by a sudden severe reduction in the tonus of the arterioles, or by a reduction in the volume of the blood. In some instances, it is caused by a decreased pumping action of the heart secondary either to damage to the heart muscle or to interference with the origin and conduction of the cardiac impulse.

Insufficient blood volume is a common cause of lowered arterial blood pressure. The cardiac output decreases, since the venous pressure, which determines ventricular filling, decreases. The cardiovascular adjustments which occur following a rapid reduction in blood volume, as from hemorrhage, are described on pages 277-278.

The blood pressure decreases sharply if the tonic vasoconstrictor influence from the centers in the medulla suddenly is suspended. The smooth muscle of the arterioles undergoes a decrease in tonus which allows them to relax, and this permits an increase in pressure in the capillaries (page 202). A greater volume of blood remains in the capillary beds and veins, particularly in those below the level of the heart, in a person in the upright position. Cardiac filling decreases, therefore cardiac output and arterial blood pressure fall precipitously. The decrease in blood flow to the brain is of such a degree that consciousness cannot be maintained. When the subject faints, the assumption of the horizontal position favors

the return of blood to the heart and tends to restore cardiac output. The restoration of circulation is even more rapid if the body is placed so that the head is below and the feet above the horizontal plane.

Cardiac Work

When a weight is lifted vertically, the work performed in doing this can be calculated simply by multiplying the weight lifted by the distance. A foot-pound of work is done if one pound is lifted one foot. In the case of the work of the heart, not only is a certain weight or mass of blood moved, but it is moved against a resistance, the pressure in the aorta, and also velocity is imparted to the blood. Hence the factors which must be considered in calculating work done by the heart are (1) the amount of blood pumped, (2) the pressure against which it is pumped, and (3) the velocity imparted to it. A change in amount of blood pumped is always associated with a corresponding change in velocity, hence these two factors are inseparable. The work of the left ventricle is increased if the cardiac output is increased, even if there is no change in arterial pressure. In arterial hypertension, ordinarily, cardiac work is increased in proportion to the increase in mean arterial pressure, since the cardiac output is normal.

The work of the right ventricle is related to the same factors as the work of the left: (1) volume of blood pumped, (2) velocity, and (3) pressure. The first two factors are essentially the same for the right ventricle as for the left, but the mean pressure in the pulmonary artery is about one-sixth the mean pressure in the aorta; therefore, the work done by the right ventricle is about one-sixth the work of the left ventricle. Under abnormal conditions, the resistance to flow in the pulmonary circuit may become greatly increased and the work of the right ventricle becomes proportionately increased if circulation is maintained.

The Arterial Pulse

A pulsation of pressure is produced at the base of the aorta during each cardiac cycle, and this causes a pulse wave to be transmitted along the systemic arterial tree. The pulse wave is a phenomenon occurring in the walls of the distended elastic blood vessels. The velocity of transmission of the pulse wave can be determined by recording its arrival at two

points at some distance apart on the same vessel, for example, at the level of the upper arm and at the wrist.

The velocity of transmission of the pulse wave is related to the caliber and elasticity of the arterial wall. The normal figure for velocity of transmission of the pulse is 5 to 9 meters per second. With aging, the arterial wall becomes less distensible, and the velocity of transmission of the pulse wave increases in proportion to the decreased distensibility. The wave is transmitted less rapidly in vessels of large caliber than in the smaller vessels; therefore, the velocity of transmission increases as the pulse wave moves outward along the arterial tree. A third factor influencing the velocity of transmission of the pulse wave is the pressure within the arterial tree; the higher the pressure, the greater the velocity of the pulse wave. It should be noted that the pulse wave is transmitted along the artery much faster than the velocity of the blood flow.

When the pulse is felt at the wrist, information is obtained concerning rate and rhythm of the heart beats, pulse pressure and strength of the heart beat, and extent of filling of the arterial tree as well as the condition of the arterial wall itself.

Chapter 23

THE CAPILLARIES AND THE VENOUS SYSTEM. FLUID COMPARTMENTS

Interchange Across the Capillary Wall

The capillary may be considered as the reason for the existence of the remainder of the circulatory system, since it is in the capillary beds that the majority of the functions of the circulatory system are performed. The capillary walls provide a very large surface or membrane separating the blood plasma from the interstitial fluid. The blood moves slowly in the capillaries, and this fact, along with the large surface involved, makes possible the adequate exchange of substances between the blood plasma and interstitial fluid. The basic mechanisms for the exchange are the physical processes already described as being concerned in the transfer of materials in solution across membranes, namely, diffusion, filtration, and osmosis (page 27).

The permeability of the capillary wall is such that all of the smaller dissolved particles such as sodium ions, chloride ions, glucose, etc., and, of course, water can readily pass through. The molecules of the plasma proteins are sufficiently large that the capillary wall acts as a barrier to them, hence the constituents of blood plasma other than protein diffuse freely back and forth between the blood plasma, while the proteins for the most part are retained in the plasma. The diffusible substances pass in both directions, but the net effect is in the direction of causing concentrations to become equal on the two sides of the capillary wall. Waste substances, such as urea and CO_2 , which are being produced in the cell, diffuse into the interstitial fluid and thence into the plasma because the concentration in the plasma is less than in the interstitial fluid. However, the concentration in the plasma can never rise to equal that in the inter-

stitial fluid as long as blood flows in the capillary. Nutrients diffuse from the plasma into the interstitial fluid and thence into the cell because the concentration of these substances in the cell is being continually reduced as they are used. The concentration of nutrients in the interstitial fluid can rise to equal that in the plasma only if the cell ceases to use these substances. Thus, it is apparent that, under physiological conditions, no equilibrium with respect to the concentrations of the waste substances and nutrients in the plasma and interstitial fluid is established; the wastes continually diffuse into the plasma and the nutrients diffuse out.

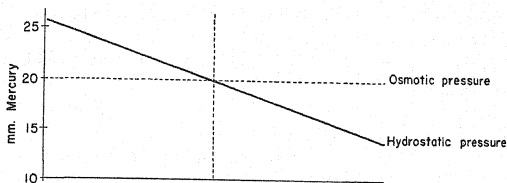


Figure 23-1. Diagram illustrating that osmotic pressure due to plasma protein remains virtually constant, while hydrostatic pressure decreases along the capillary.

At the arteriolar end of the capillary, hydrostatic pressure normally exceeds osmotic pressure; at some point along the capillary, indicated by the vertical broken line, the two forces are balanced, and at the venous end, osmotic pressure exceeds hydrostatic pressure. Hydrostatic pressure is subject to wide variations as arteriolar tonus changes. (From Youmans' *Basic Medical Physiology*.)

The net exchange of water across the capillary wall is in the direction of a loss from the plasma into the interstitial space. Although water molecules are free to diffuse in each direction, this *net* loss of water is not related to diffusion, since the concentration of water molecules is not greater in the plasma than in the interstitial fluid. The net loss of water from the capillary into the interstitial space is caused by *filtration*. As previously explained, filtration of a solvent occurs when there is a difference in pressure on the two sides of a barrier which is permeable to the solvent. There is hydrostatic pressure in the capillary which is the residuum of the pressure produced by the ejection of blood from the left ventricle into the aorta. The pressure ranges around 25 mm. of mercury at the arteriolar end of the capillary down to about 15 mm. of mercury at the venous end when the smooth muscle of the arteriolar wall is in a state

of moderate tonus. The effect of this hydrostatic pressure, tending to cause filtration of water and all dissolved substances through the capillary wall, is in part counteracted by osmotic pressure acting in the opposite direction. Since the protein is present in greater concentration in the blood plasma than in the interstitial fluid, the osmotic tension of the plasma exceeds that of the interstitial fluid by about 20 mm. of mercury. Thus, at the arteriolar end of the capillary, the pressure promoting filtration exceeds the opposite effect of the plasma protein (by about 5 mm. of mercury), hence water is lost from the plasma. At the venous end, on the other hand, the osmotic effect is more than sufficient to counteract the hydrostatic effect and water is returned to the plasma. However, a moderate degree of arteriolar dilatation will cause a rise in pressure all along the capillary, so that it is possible for filtration to occur over the entire length of the capillary, and vasoconstriction will have the opposite effect. The fluid which does not return to the capillary is free to pass into the lymph system which supplements the drainage function of the venous system.

Lymphatic system. All of the lymph from the legs and abdominal organs, including the digestive tract, drains into the *thoracic duct* which lies in front of the bodies of the thoracic vertebrae. The thoracic duct drains lymph from the chyle cistern in the abdomen and empties into the venous system at the junction of the left internal jugular and left subclavian veins. The right arm and right side of the head and thorax are drained by a lymph duct which empties into the venous system at the junction of the subclavian and internal jugular veins on the right. The lymph drains through nodes which have the dual function of filtering any harmful materials from the lymph and of producing the lymphocytes.

Edema refers to the presence of abnormally large amounts of interstitial fluid. It is a manifestation of several types of disease. Fundamentally, an increase in interstitial fluid is produced by increased rate of loss through the capillary wall or failure of drainage. A disturbance of the balance of forces controlling movement of fluid across the capillary wall in the direction of increasing the rate of loss from the capillary would result (1) if the hydrostatic pressure in the capillary is increased, (2) if the plasma protein level is decreased, or (3) if the permeability of the capillary wall is increased. Obstruction of venous drainage from a part may produce moderate degrees of edema, and severe localized edema is produced when both lymphatic and venous drainage of the part are obstructed.

Venous Return and Venous Pressure

Role of arteriolar tonus. The capacity of the capillaries is determined mainly by the pressure within them, since they are distensible. If the arterioles become dilated, the volume in the capillaries becomes increased and both the arterial pressure and volume of blood in the venous system decreases. Since the venous return determines the amount of blood available for the heart to pump, a decrease in venous return is associated with a decrease in cardiac output. Thus, a failure of the circulation can occur if there is excessive "pooling" of the blood in the capillary beds. Under normal conditions, this is prevented by the maintenance of arteriolar tonus. The volume of blood in the veins is related also to the total volume of blood in the circulatory system. Transfusion of blood causes an elevation of the venous pressure and during hemorrhage the venous pressure decreases.

When venous return suddenly decreases, as in hemorrhage, or when there is severe vasodilatation, compensatory mechanisms are activated which tend to restore the venous pressure. The smooth muscle in the walls of the larger veins contracts. This *venomotor* response appears to be elicited on a reflex basis from the fall in pressure in the carotid sinuses. Simultaneously, reflex arteriolar constriction elicited from the same receptors serves to decrease pressure and volume in the capillary beds. In carnivores and, to a lesser degree in man, the spleen undergoes a reduction in volume when arterial and venous pressure decrease.

Effects of muscular activity. An important mechanism in the maintenance of the venous return in a person in the upright position is the pumping action on the large veins in the legs during contraction of the skeletal musculature. The veins of the extremities are equipped with a number of valves which function much like the cardiac valves. When a segment of vein between two valves is compressed from without by the contraction of skeletal muscle, blood is forced toward the heart. Also, the valves prevent any backflow which would be produced by gravity. Since the valves of the leg veins subdivide the long column of blood into a series of small columns, the hydrostatic pressure on each valve is small. If the valves were not present, the capillaries of the feet would be subjected continuously to the hydrostatic pressure produced by the entire column of blood when one is in the standing position. This pressure would be sufficient to force excessive amounts of fluid out into the interstitial

spaces, and swelling of the feet would result. When a section of a vein becomes enlarged, or varicose, the edges of the valve leaflets do not come together, and this increases the pressure against the next valve below. Even when the veins of the legs are anatomically normal, the feet and

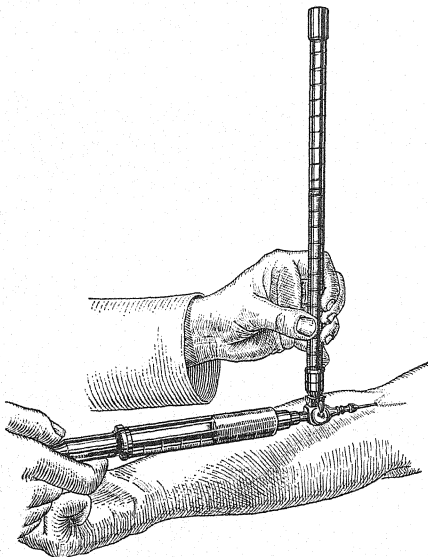


Figure 23-2. Apparatus for direct measurement of venous pressure.

ankles may become severely swollen due to accumulation of interstitial fluid when a person remains in the sitting or standing position for prolonged periods.

Measurement of venous pressure. The pressure in the medium-size and large veins ranges from about 12 cm. of water down to around atmospheric pressure. The pressure in the veins on the back of the hand (in a thin person) can be estimated fairly accurately simply by raising the hand very slowly from a point below the level of the heart until the veins

barely collapse. The vertical distance from this level down to the approximate level of the right atrium is the venous pressure in centimeters of blood (which may be considered to be the same as water as far as this measurement is concerned).

Venous pressure is measured directly by inserting a hypodermic needle into the vein and allowing physiological saline to run in through the

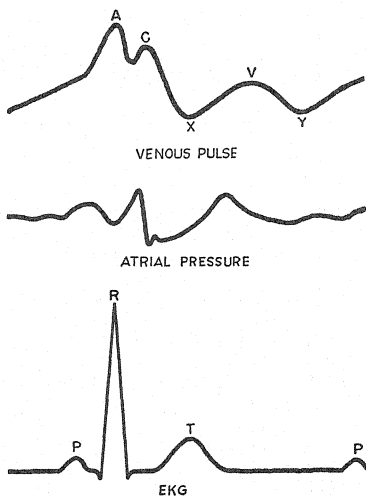


Figure 23-3. Correlation of venous pulse, right auricular pressure, and the electrocardiogram.

(From Youmans' *Basic Medical Physiology*.)

needle from a perpendicularly placed glass tube. The level of the saline ceases to fall when the pressure in the column of liquid is balanced against the pressure in the vein. The vertical distance from the level of the saline in the tube to the approximate level of the right atrium, measured in centimeters, is the venous pressure. By measuring down to the level of the right atrium rather than to the site of the needle, one corrects

for the pressure in the vein due to the effects of gravity; the reading obtained is the pressure in the vein in excess of that caused by gravity.

Venous Pulse

Pulsation of the external jugular vein may be observed at the base of the neck just above the collar bone. Usually, there are three prominent pulsations with each heart beat. This venous pulsation is a reflection of pressure changes occurring in the right atrium. In Figure 23-3 curves correlating the changes in pressure in the right atrium and the pulsations in the jugular vein during the cardiac cycle are shown. The A wave of the jugular pulse occurs synchronously with auricular systole, the C wave occurs synchronously with the beginning of ventricular systole, the V wave develops toward the end of ventricular systole. Since there are waves in the jugular pulse associated with both auricular systole and ventricular systole, observation of the venous pulse may provide information about the cardiac rhythm; however, at the present time this type of information usually is obtained from the electrocardiogram.

Fluid Compartments

Basis for fluid compartments. Water constitutes about two-thirds of the total weight of the body. The water of the body is subdivided into two main compartments, intracellular fluid and extracellular fluid, and the latter compartment is further subdivided into the interstitial fluid and the water of the blood plasma. The blood volume is roughly two times the plasma volume, since about 45 per cent of the blood consists of cells.

The basis for the final separation into three fluid compartments is the fact that there are two main barriers which allow water to pass freely, but which do not allow certain dissolved substances to pass. These barriers are the capillary wall and the cell wall. The capillary wall is a barrier in some degree with regard to protein, and other constituents of plasma are free to pass; hence the composition of blood plasma and interstitial fluid are similar except in their protein content. The cell wall does not allow Na^+ or K^+ to become equally distributed outside and inside the cell. Sodium is found in large amounts in the blood plasma and interstitial fluid and in small amounts in the intracellular fluid. Potassium is present in large amounts in intracellular fluid and in small amounts in the extra-

cellular fluid. The presence of this small amount is, however, of great importance (page 370). The diagram in Figure 23-4 serves to emphasize the bases for the fluid compartments. In this diagram, it is also illustrated that the osmotic tension of the plasma, due to plasma protein, exceeds that of the interstitial fluid and thus helps to maintain the volume within the circulatory system, in spite of the fact that hydrostatic pressure is being exerted to force fluid out into the interstitial space.

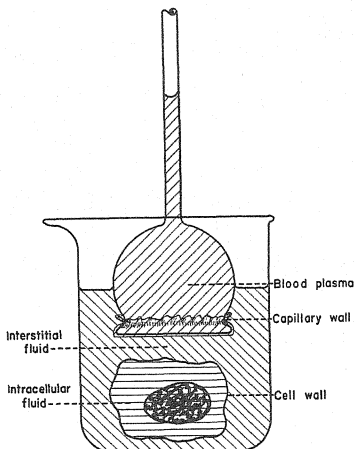


Figure 23-4. Diagram illustrating basis for the principal fluid compartments.

(From Youmans' *Basic Medical Physiology*.)

Measurement of fluid compartments. The blood volume may be determined by injecting into the circulation a known amount of a suitable dye which will not pass through the capillary walls. After the injected substance has become thoroughly mixed, a certain amount of blood is withdrawn, and the amount of the substance in this sample is determined. From this information, one can calculate the volume in which the dye has become distributed. For example, if one mixes 1000 mg. of a substance in an unknown volume of water, then withdraws one milliliter and

finds that it contains one milligram, it is evident that the volume of the water is 1000 ml. (one liter). If one determines the blood volume and the hematocrit (page 177), he can calculate the plasma volume. In normal subjects, it is approximately one-half the blood volume.

Extracellular fluid volume also can be measured, using the dilution principle described above, if a substance is injected that will pass through the capillary wall, but not through the cell wall. To measure the total body water, a substance, like water itself, which will pass through both

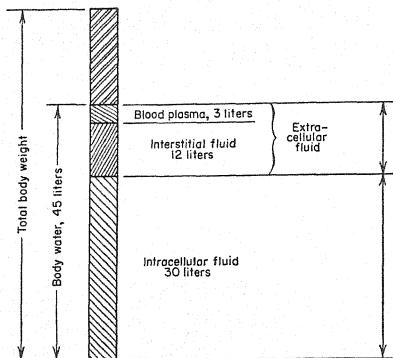


Figure 23-5. Comparative volumes of the fluid compartments in an adult of average size.

the capillary wall and the cell wall is injected. Heavy water (D_2O) has been used for this purpose. The volume of the intracellular fluid can be calculated by subtracting the volume of the extracellular fluid from the volume of the total body water.

Variations in Volume of Fluid Compartments

Body water. The total amount of water in the body is maintained relatively constant in the normal person, even though there are wide variations in the amount ingested and in the rate of loss from the skin by perspira-

tion. The control of the hydration of the body is accomplished largely by changes in rate of renal excretion of water. Any excess of water over the amount required to maintain the normal degree of hydration is eliminated by the kidney. For example, if one drinks three pints of water when the stomach is empty, the water will be absorbed rapidly and about three pints of urine containing negligible amount of solutes will be excreted within the next three or four hours. The mechanism for this is considered on page 382. If the intake of water is restricted, thirst becomes intense and thus one is stimulated to ingest an adequate amount of water to meet the needs of the body. Water is needed primarily to replace that which inevitably is lost by evaporation from the skin surface and in the exhaled air, and to provide a minimum amount of water to be excreted with wastes in the urine. If less than this amount is drunk then dehydration and thirst result.

Water can move freely through the capillary walls and cell walls, and its distribution between the fluid compartments is determined by the laws of diffusion, filtration, and osmosis. A decrease in body water, in addition to restriction of intake, may be produced by excessive loss from the bowel, as in severe diarrhea, excess excretion by the kidney, and by excessive perspiration. Also, fluid may be lost directly from the blood stream by hemorrhage or transudation.

Blood volume. The blood volume also is maintained within a restricted range in the normal person. If blood is withdrawn, the previous volume is restored and, if blood is transfused into an individual who has a normal blood volume, the excess is removed. The restoration of the normal levels requires a few days or weeks depending upon whether the alteration being combatted is mild or severe. Generally, it is considered that it is safe to remove a pint of blood from a donor about every six weeks for several times; however, the iron intake must be increased and the hemoglobin content checked before each bleeding. The mechanisms for the maintenance of the proper volume of blood for the holding capacity of the circulatory system are not as clear as the mechanism for regulation of body water, although they are in part the same. The most important organs involved in the regulation of blood volume are the kidneys, the liver, and the bone marrow.

Hemorrhage. That the bone marrow is stimulated to restore the erythrocytes after hemorrhage already has been discussed (page 178). The liver also is stimulated to increase its production of plasma proteins. Changes in renal function after hemorrhage include a decreased excretion

of NaCl and water, and this aids in the restoration of plasma volume as the subject continues to ingest NaCl with meals.

Another mechanism that counteracts the fall in blood volume during hemorrhage and contributes to restoration of the volume after hemorrhage is related to the decreased hydrostatic pressure in the capillaries. The reduction in hydrostatic pressure occurs both directly because of the decreased blood volume and because of a reflex constriction of the arterioles elicited by the fall in pressure in the carotid sinuses and aortic arch. The hydrostatic pressure being considerably lowered and the osmotic tension of the blood due to plasma protein remaining relatively constant, the balance of forces across the capillary wall is changed in the direction of favoring transfer from the interstitial spaces into the blood stream. To a lesser degree, fluid may be transferred from the cells into the interstitial space. The change just described sometimes is of diagnostic value. For example, if bleeding is internal, as from a ruptured spleen, and the diagnosis is in question, repeated hematocrit determinations can be made and a progressive decrease in the per cent of red cell volume will occur as the blood becomes diluted with interstitial fluid.

In severe hemorrhage, there are immediate responses which serve to maintain the circulation to vital organs, in spite of the decreased blood volume. The decrease in pressure in the carotid sinuses and aortic arch elicits, reflexly, constriction of arterioles in the skin and abdominal viscera, so that a greater fraction of the cardiac output will flow through the central nervous system and other vital structures. The pulse pressure is decreased in hemorrhage because of the increase in heart rate, which allows less time for ventricular filling, and because of the decreased head of venous pressure.

Shock. The term *shock* commonly is used to designate a syndrome which develops when there is a chronic, severe decrease in the circulating blood volume. Since blood volume can be reduced in numerous ways, the clinical conditions leading to shock are many. Among these are transudation from burned or injured areas, diarrhea, hemorrhage, etc. Regardless of the cause, the basic syndrome seen in shock is relatively constant since it is produced by the lowered circulating blood volume. Shock of this type is treated by blood and plasma transfusions until the blood volume is restored to adequate levels.

Chapter 24

MECHANICS OF BREATHING

Need for Exchange of Oxygen and Carbon Dioxide

Living cells use oxygen in the exothermic reactions essential to the maintenance of life, and carbon dioxide is liberated as a waste product; therefore, the cells must have an adequate supply of oxygen and the carbon dioxide must be removed. In the case of single-celled aquatic organisms, the exchange of gases is accomplished simply by diffusion. The water in which the organism lives has an oxygen tension approaching that of the atmospheric air to which the water is exposed. In proportion to the rate of utilization of oxygen by the cell, the oxygen tension of the cell is reduced below that of the surrounding water, and, consequently, oxygen diffuses from the water into the cell. The oxygen tension of the water is maintained in turn by diffusion of oxygen into the water from the air. As the cell produces carbon dioxide, the tension of this gas in the cell exceeds that in the water; carbon dioxide diffuses out of the cell into the water and from the water into the air.

In organisms consisting of large numbers of cells, the problems of oxygen supply and carbon dioxide removal are more complex. In an aquatic organism consisting of a number of cells, oxygen diffuses from the water into the peripherally located cells and on into the centrally located cells, since the tension in the latter is lower than in the former. The larger the mass of cells composing an organism, the lower would be the oxygen tension in the cells which are centrally located. On the other hand, if channels were present between the cells, so that the water could circulate through the mass, all of the cells could maintain an oxygen tension approaching that of the water. The capillaries of the circulatory system of higher organisms correspond to such channels. The oxygen tension in the blood reaching the capillaries is determined by the oxygen tension to which the blood is exposed in the lungs as it passes

through the pulmonary capillaries. The oxygen tension in the terminal air passages of the lungs under normal conditions is related to two factors: (1) the oxygen tension in the inspired air, and (2) the rate and depth of breathing. It is apparent that the maintenance of a normal oxygen tension in the capillaries, and hence in the tissues, depends upon both the respiratory and the circulatory systems. A deficiency on the part of either of these systems may be reflected in changes in oxygen and carbon dioxide tension in the tissues. Therefore, it is understandable that the mechanisms which control circulation and respiration are closely integrated. For example, the demands upon these two systems are simultaneously increased when the oxygen supply is inadequate, and in this case mechanisms by means of which cardiac output and the breathing effort are increased are brought into activity. Furthermore, if either the respiratory system or the circulatory system is impaired, adjustments which are of compensatory value occur in the other system.

Physiological Anatomy

The respiratory tract is composed, consecutively, of the nasal passages, nasopharynx, larynx, trachea, bronchi, and lungs. The trachea, or windpipe, divides into right and left bronchi, which are the air conduits supplying the right and left lungs. Each bronchus divides repeatedly until the branches become fine tubes known as *bronchioles*. The walls of the bronchioles are composed of a thin layer of elastic tissue and smooth muscle and are lined by ciliated epithelium. The actual functional unit of the lung is the lobule, which is the structure supplied by a single bronchiole. The bronchiole leads into an intricate pattern of passages and blind sacs providing a large surface for exchange of oxygen and carbon dioxide between the blood and the contained gas mixture; the passages, consecutively, are alveolar ducts, atrium, alveolar sacs, and alveoli. These are labeled in Figure 24-2.

The pulmonary artery and pulmonary veins follow the air passages from the bronchi to the alveoli, so that there are three separate intertwining branching "trees." Blood enters the pulmonary artery from the right ventricle and flows to the capillaries which make up part of the alveolar wall, and then it returns to the left auricle by the pulmonary veins. The lung tissue also receives blood from the systemic circuit by branches from the bronchial arteries; this provides oxygenated blood for

those structures in the lungs which do not lie close enough to the air passages to permit sufficient gaseous interchange simply by diffusion. The blood which flows into the lungs from the bronchial arteries passes on into the same capillary bed which receives blood from the pulmonary arteries and returns to the heart by the pulmonary veins.

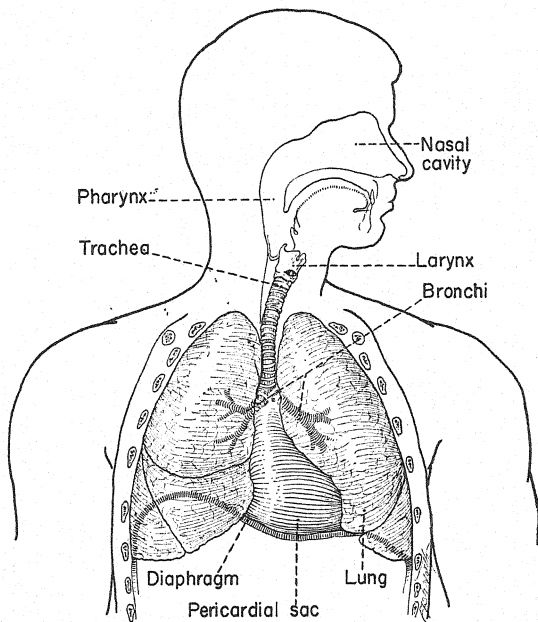


Figure 24-1. Parts of the respiratory system.

The smooth muscle in the walls of the air passages (page 286) and of the smaller blood vessels has an efferent innervation from each of the two divisions of the autonomic system. Also, the lung substance is provided with receptors and afferent nerves which are influenced by changes in the degree of distention of the lungs.

Each lung is contained in a separate closed sac which has fibrous walls lined with a serous membrane. The layer on the lung surface is the *visceral* pleura and the outer layer which lies against the inner aspect of the thoracic wall is the *parietal* pleura. The potential space between these layers is the pleural space. Inflammation of the pleura is known as *pleurisy*.

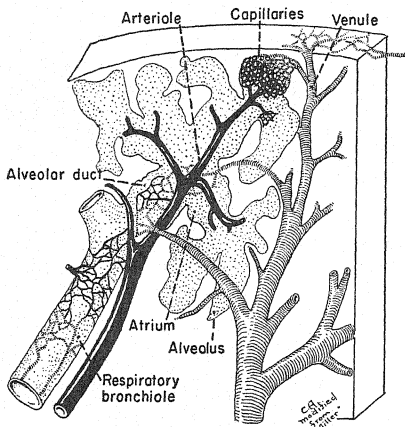


Figure 24-2. Terminal air passages of the respiratory tree.

(By permission, after Miller, *The Lung*. Copyright, 1947, by Charles C Thomas Publishers.)

One of the functions of the pleura, similar to that of the pericardium, is to provide moist layers which permit two contacting surfaces to slide back and forth with negligible friction and without irritation. In pleurisy, the inflamed membranes are irritated by movement against each other and characteristic pain may be associated with each respiratory act.

Mechanics of Inspiration and Expiration

The term respiration, used in the more general sense, refers to the processes by means of which oxygen is taken up by living cells and used

in oxidative processes. Breathing, or respiration in a more limited sense, is the process by which air is moved in and out of the lungs. The act of breathing consists of rhythmic contractions of muscle groups which serve to enlarge the capacity of the thoracic cage and thus draw air into the lungs and then permit it to be expelled. The former phase is called inspiration and the latter expiration. The mechanics of breathing can be illustrated by a model as shown in Figure 24-3.

A large bottle is prepared with the bottom removed and replaced by a rubber diaphragm as shown in the figure. A three-hole rubber stopper is placed in the bottle and pieces of glass tubing are passed through two

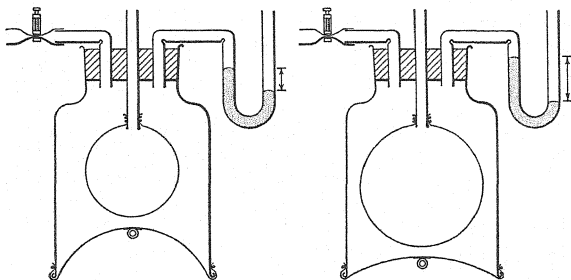


Figure 24-3. Model to illustrate mechanism of breathing.

of the holes. A balloon is tied on the end of one of the pieces of glass tubing and a segment of rubber tubing and a clamp are placed on the other as diagrammed and the stopper is inserted into the mouth of the bottle so that the balloon is inside the bottle. A U-tube manometer is inserted in the third hole. Now, air is sucked out through the tubing which is equipped with the clamp, and, as the pressure in the space between the glass and the balloon is decreased below the atmospheric level, air will enter and distend the balloon. Simultaneously, the rubber diaphragm will be drawn upward, since the pressure above it is less than the (atmospheric) pressure below it. When the desired amount of air has been removed from the "pleural" space between the balloon and the wall of the bottle, the clamp is tightened so that air cannot enter. At this stage, the conditions which exist when the chest is in the end-expiratory position are simulated. A pressure which is equal to the atmospheric pressure

level is exerted throughout the air passages, while the pressure in the pleural spaces is subatmospheric.

The mechanism of *inspiration* can be illustrated by pulling downward on the handle attached to the rubber diaphragm. The pressure in the "pleural" space on the outside of the wall of the balloon is decreased further as the diaphragm descends, while atmospheric pressure still is being transmitted to the inside of the balloon; therefore, air will enter the balloon. Expiration is simulated when the pull on the handle is released; the pressure in the "pleural" space will rise again to the resting subatmospheric level and air will pass out of the balloon. Thus, to draw air into the balloon, work is performed; whereas, on releasing the handle, air passes out of the balloon simply as a result of the physical characteristics of the system. This is the situation in normal, quiet breathing or *eupnea*. A muscular effort serves to enlarge the thoracic cage. This is accomplished by a downward movement of the dome-shaped diaphragm and an upward and outward movement of the ribs produced in part by contraction of the external intercostal muscles. As the thoracic cage enlarges, air is drawn into the elastic lungs. When the muscular effort ceases, the expiratory position of the diaphragm and ribs is resumed as the air passes out of the lungs.

In exercise, there are demands for a greatly increased pulmonary ventilation, or *hyperpnea*. In this case, the strength of inspiration is greatly increased both by a greater degree of activity of the muscles used in eupnea and by activation of accessory inspiratory muscles; and expiration is no longer passive, since muscles are activated which accelerate the emptying of the lungs.

Volume Relationships in the Air Passages

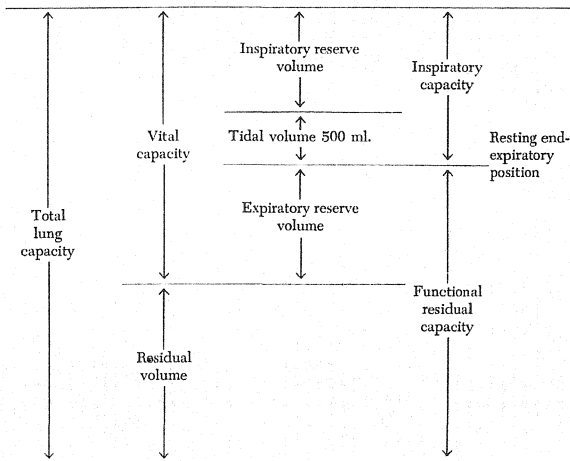
In an adult of average size, 400 to 500 ml. of air are inhaled and exhaled during each respiratory cycle. The volume moved per cycle is known as *tidal air*. The total volume of air breathed per minute is known as the *respiratory minute volume* (RMV).

The greatest volume of gas that can be inhaled beyond the normal inspiration is called the *inspiratory reserve volume* (formerly known as complementary air), and the deepest exhalation beyond the normal exhalation is the *expiratory reserve volume* (formerly known as supplemental air). *Inspiratory capacity* is the volume of air that can be inhaled

from the end-expiratory position. It includes the tidal air plus the inspiratory reserve volume. The total volume of air that can be exhaled from the lungs following a maximal inspiration is the *vital capacity*. The vital capacity of a normal adult of medium size lies between 3500 and 4500 ml. The volume of gas that remains in the lungs at the end of the maximum expiratory effort is the *residual volume*. Finally, total lung capacity is the total volume of air contained in the lungs at the end of the maximal inspiratory effort.

Vital capacity shows considerable variation from one individual to another; but, normally, it remains relatively constant in a given individual. The vital capacity tends to be reduced by anything which occupies space in the thoracic cavity and thus encroaches upon the space normally occupied by the lungs. Anything that increases the volume of the abdominal contents or the pressure in the abdominal cavity interferes with the descent of the diaphragm and hence decreases vital capacity. A direct cause of a decreased vital capacity is weakness of the respiratory musculature or damage to the nerves which innervate the respiratory muscles.

Nomenclature of Lung Volumes



Control of Smooth Muscle in the Bronchioles

Smooth muscle is found in the walls of the entire bronchial tree down to the bronchioles. The bronchiolar smooth muscle is so well developed in some animals, such as the guinea pig, that it is capable under certain conditions of acting as a sphincter which completely closes the bronchiole

and prevents ventilation of the alveoli. This occurs in the anaphylactic reaction in guinea pigs, as previously described in the discussion of antigens.

The smooth muscle in the walls of the bronchioles is innervated by inhibitory adrenergic fibers derived from the sympathetic system and excitatory cholinergic fibers from the vagus nerves. The bronchioles are constricted by acetylcholine and histamine and are relaxed by epinephrine.

The bronchiolar smooth muscle has a protective function, since it tends to constrict reflexly when irritating vapors are inhaled and thus supplements the cough reflex in preventing the entrance of the irritant into the alveoli.

Also, it appears that the bronchi-

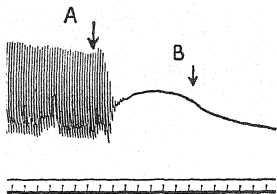


Figure 24-4. Production of bronchiolar constriction by histamine.

The lungs of a guinea pig are ventilated by rhythmically forcing air into the trachea. The record shows fluctuations in volume of the lungs. Following histamine injection at A, first arrow, the bronchioles close completely, so that air can neither enter nor leave the alveoli. At B, second arrow, atropine was injected, but bronchiolar spasm was not relieved. The histamine-induced spasm can be relieved by epinephrine. (By permission, after Wright from Dale and Laidlaw, *J. Physiol.*, 41:335, 1910.)

olar smooth muscle undergoes a decreased tonus during inspiration and an increased tonus during expiration and thus aids in ventilation of the alveoli under physiological conditions. This problem has been difficult to study, since similar changes in caliber would occur on a passive basis during the respiratory cycle.

Frequently, in individuals having *bronchial asthma*, the bronchioles have become sensitized to foreign protein. When the antigen reaches the bronchioles, usually by inhalation, the antigen-antibody combination in the smooth muscle cells causes contraction. Also, in asthma the mucosa of the respiratory passages frequently becomes swollen and this contributes to further obstruction of the

bronchioles. Air is drawn into the lungs on inspiration, but cannot be expelled simply by the passive processes that are sufficient for expiration in normal, quiet breathing. Consequently, the alveoli are overdistended and poorly aerated. In bronchial asthma, as in any situation where the ventilation of the alveoli is decreased, the oxygen content of the alveolar air is lowered and the carbon dioxide tension is increased.

Chapter 25

UPTAKE AND TRANSPORT OF RESPIRATORY GASES

The sequence of events concerned in the supplying of oxygen to the tissues and the removal of CO_2 is as follows. Oxygen in the air is breathed into the pulmonary alveoli where it diffuses into the pulmonary capillaries to be carried by the pulmonary veins back to the left side of the heart. The left ventricle pumps the oxygen-rich blood to the systemic capillary beds where oxygen is given off to the tissues and carbon dioxide is taken on by the blood. The blood returning to the right atrium is relatively low in oxygen content and high in CO_2 content. This blood is pumped from the right ventricle through the pulmonary arteries to the lungs, and here CO_2 is given off and oxygen is taken up; thus, the cycle is completed. Breathing, as already described, is the mechanical process by means of which the CO_2 content of the alveolar air is kept down and the O_2 content maintained. The O_2 content of alveolar air can never equal that of atmospheric air since the oxygen in the alveoli is constantly being absorbed. The CO_2 content of the alveolar air must always be higher than the level in the inspired air, since CO_2 is being produced continuously. The exchange of O_2 and CO_2 between alveolar air and the blood in the pulmonary capillaries sometimes is known as *external* respiration, while the interchange of the respiratory gases between the blood of the systemic capillaries and the tissues is referred to as *internal* respiration.

Composition of Atmospheric Air and Alveolar Air

As explained on pages 22–25, the amount of a given gas present in a mixture may be expressed either in terms of volumes per cent or as partial pressure (tension). The per cent composition of the gas mixture gives

information concerning the *ratio* of the number of molecules of one gas to the number of molecules of all of the other gases in the mixture, but it does not indicate the *actual* number of molecules of a gas in a given volume. The figure for partial pressure or tension, which is obtained by multiplying *per cent* (by volume) *times total pressure*, does provide information concerning the number of molecules of the gas per unit volume, and it is this figure which is important in physiological studies.

At sea level, the barometric pressure ranges around 760 mm. of mercury. The oxygen content of dry atmospheric air is 20.94 per cent. The volume per cent of air containing water vapor is only slightly less than this, since the water vapor tension is only 47 mm. of mercury when the air is saturated with water vapor at body temperature. At lower temperatures, the vapor tension becomes lower for any given per cent saturation. The partial pressure of oxygen in dry atmospheric air at sea level is $20.94 \text{ per cent} \times 760 = 159$ or, in round numbers, 160 mm. of mercury. In air containing water vapor, it may be closer to 150. The per cent of CO_2 in atmospheric air is only 0.04; and, as far as influences on breathing are concerned, this may be disregarded. The remaining 79 per cent of dry atmospheric air consists of gases which are inert as far as effects on the body are concerned. About 78 per cent of the inert gases is nitrogen and the remainder is argon with traces of other gases.

The barometric pressure decreases progressively with altitude. In Figure 25-1 the relation of pressure to altitude is graphed. Observe that the barometric pressure at 18,000 ft. altitude is about 380, or one-half that at sea level. Since the O_2 per cent is the same at all altitudes, the O_2 tension decreases in direct proportion to the decrease in barometric pressure. The oxygen tension is 20.94 per cent of the total barometric pressure at each altitude indicated.

The alveolar air in a given individual under resting conditions, and in the absence of any voluntary control of his breathing, remains relatively constant. The reasons for this are presented in the description of the mechanisms for regulation of ventilation rate. A sample having the composition of alveolar air may be obtained if a subject suddenly exhales forcibly at the end of a normal expiration (as for measuring expiratory reserve volume) and the last 100 to 200 ml. of the exhaled air is collected. In other words, it has been found that the last 100 to 200 ml. of the expiratory reserve volume has a composition which is approximately that of alveolar air. The first part of the exhaled air, coming from the larger air passages, is intermediate between alveolar and atmospheric air in its

O₂ and CO₂ content, but this is washed out as expiration proceeds until the last portion having approximately the composition of alveolar air is obtained. It is apparent that if *all* of the expired air is collected, rather than the last portion, this will have an O₂ and CO₂ composition which is intermediate between atmospheric and alveolar air.

The alveolar air collected in a suitable container can be transferred into a calibrated glass burette, then it can be exposed first to a chemical which absorbs the CO₂ and subsequently to a chemical which absorbs the O₂. It is convenient to start with 100 ml. of alveolar air (saturated with water

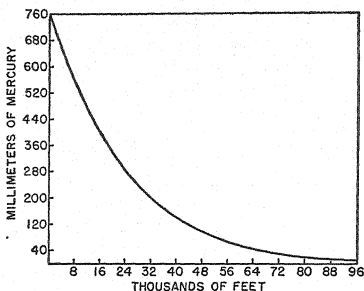


Figure 25-1. Relation between barometric pressure and altitude.

The oxygen tension at any given altitude is 20.94 per cent of the barometric pressure.

vapor), so that when the CO₂ and O₂ are absorbed one gets directly the per cent of each of these gases in the alveolar air which also is saturated with water vapor. It is found that the 100-ml. sample shows a 5.3 (± 1) ml. decrease in volume when the CO₂ is absorbed and a further decrease in volume of about 14.5 ml. when the O₂ is absorbed. Hence the tensions of these gases in alveolar air of the subject at sea level are:

$$\text{CO}_2 = 5.3\% \times 760 = 40 \text{ mm. Hg}$$

$$\text{O}_2 = 14.5\% \times 760 = 110 \text{ mm. Hg}$$

The water vapor in alveolar air is around 45 mm. of mercury. If the sum of the O₂ tension, CO₂ tension, and vapor tension is subtracted from 760, it is found that the pressure exerted by nitrogen and other inert gases in the alveoli is around 565 mm. of mercury.

As one ascends to higher altitude and continues to breathe atmospheric air, the total pressure in the alveoli decreases proportionately with the

decrease in barometric pressure. The amount of CO_2 being produced by the body, however, continues at essentially the same rate and at moderate altitudes the breathing is not significantly stimulated; hence the alveolar CO_2 tension remains about the same as at sea level. It can be visualized readily that since the CO_2 tension in the alveoli is maintained, while the total pressure in the alveoli is considerably decreased, the *per cent* of the pressure in the alveoli due to CO_2 is greatly increased. Furthermore, the O_2 tension in the alveoli is decreased because of the decrease of barometric pressure and because of the greater dilution with CO_2 (and water vapor which also remains constant); hence the *per cent* of O_2 in alveolar air also is greatly decreased.

During ascent to high altitudes, it is the lowering of the oxygen tension in the alveoli and the consequent decrease in oxygen supply in the systemic arterial blood which causes impairment of the body functions. If, at high altitudes, oxygen is breathed instead of air, the tension of oxygen in the lungs may be increased; however, at very high altitudes, the oxygen tension in the alveoli is subnormal even when 100 per cent oxygen is breathed. It is evident, for example, that if the total barometric pressure is only 110 mm. of mercury, the maximum O_2 pressure of inhaled air, as when 100 per cent oxygen is breathed, could be only 110 mm. of mercury, but the pressure in the alveoli would be much less than 110, since the CO_2 tension plus the water vapor tension would still be about 80 mm. of mercury. The O_2 tension in the alveoli, therefore, could not significantly exceed 30 mm. of mercury under these conditions, and the subject would be suffering from severe oxygen lack in spite of breathing 100 per cent oxygen.

The magnitude of the differences in composition between atmospheric air and alveolar air, metabolic rate being constant, is related directly to breathing. Any increase will be reflected in a decrease in CO_2 tension and an increase in O_2 tension in the alveoli, so that the composition of alveolar air changes to approach more closely that of atmospheric air. Breath-holding, on the other hand, will cause a severe decrease in the oxygen tension and a moderate rise in the CO_2 tension in the alveoli.

Transport of Oxygen

The amount of oxygen that a given amount of blood can absorb and transport is related in the first place to the tension of oxygen to which it is exposed and in the second place to the composition of the blood. The

relationship of uptake of oxygen by the blood to the oxygen tension to which it is exposed is presented graphically in Figure 25-2. This curve is known as the *oxyhemoglobin dissociation curve*. In the graph, it is illustrated that at any specific oxygen tension to which blood is exposed only part of the hemoglobin will be combined with oxygen and part will not be combined until a tension of around 110 mm. of mercury is reached,

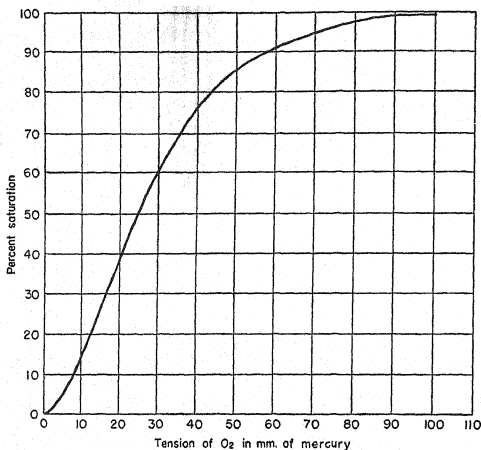


Figure 25-2. Oxyhemoglobin dissociation curve in the presence of a CO_2 tension of 40 mm. of mercury.

(From Youmans' *Basic Medical Physiology*.)

and at this level virtually all of the hemoglobin is oxygenated. It should be recognized that the dissociation curve simply indicates the *per cent* of the hemoglobin that is oxygenated at a given tension; it does not give information specifically concerning the amount (i.e., milliliters) of oxygen taken up by the blood. For this information, one must also know the amount of hemoglobin per 100 ml. of blood.

When blood is exposed to oxygen at a given tension, only a small part of the O_2 taken up by the blood is dissolved in the plasma, since oxygen

is only slightly soluble in water. Most of the oxygen absorbed by the blood is that which enters into combination with hemoglobin, hence any difference in the ability of different samples of blood to take up oxygen is related mainly to differences in the hemoglobin content. On the average, 100 ml. of blood having a normal hemoglobin content is capable of taking up about 20 ml. of oxygen. Blood from severely anemic patients will take up only a fraction of this amount.

In Figure 25-2 it may be seen that virtually all of the hemoglobin in blood is combined with oxygen, when blood equilibrates with an oxygen tension of 110 mm. of mercury such as is found in the alveolar air of normal subjects. In a normal individual, the oxygen tension in the alveoli may be increased at least four times by allowing him to breathe oxygen, but there is only a negligible increase in the amount of oxygen taken up by the hemoglobin. There is a fourfold increase in the amount of oxygen dissolved in the plasma, but this represents an actual increase of only about 1.3 ml. per 100 ml. of blood. In other words, the affinity of hemoglobin for oxygen is such that there is almost 100 per cent utilization of its capacity to take up oxygen at the oxygen tension to which the blood normally is exposed in the lungs. Next, it can be seen from the shape of the curve that the per cent of hemoglobin which remains combined with oxygen decreases rapidly as hemoglobin is exposed to lower and lower oxygen tensions. Therefore, as blood flows through a tissue which is using oxygen and hence has a lower oxygen tension than the arterial blood, oxygen will diffuse from the blood into the tissue until the oxygen tension of the blood approaches that of the tissue. As this occurs, a certain per cent of the hemoglobin gives up oxygen. For example, if the oxygen tension of the blood is lowered from 110 mm. of mercury to 30 mm. of mercury as it passes through a given capillary bed in the systemic circuit, the per cent of hemoglobin present in the oxygenated form will be decreased from about 98 per cent to about 60 per cent; approximately two-fifths of the hemoglobin will give up its oxygen, and the other three-fifths will remain oxygenated. Since each 100 ml. of arterial blood with an average hemoglobin content normally contains about 20 ml. of oxygen and most of this is combined with hemoglobin, in the example presented approximately two-fifths of 20, or 8 ml. of oxygen, would be given off to the tissue per 100 ml. of blood flowing through it. This much oxygen, or even more, is given off in very active tissues such as the heart muscle, but much smaller amounts are given off in less active tissues and in organs such as the kidney in which there is a

very high rate of blood flow. Usually, under resting conditions, the so-called *mixed venous blood* returning to the right auricle contains around 14 to 15 ml. of oxygen per 100 ml. of blood, while the blood returning to the left ventricle from the lungs contains 19 to 20 volumes per cent of oxygen. Hence approximately 5 ml. of oxygen on the average is delivered to the body by each 100 ml. of blood pumped into the systemic circuit.

At the same time that there is liberation of oxygen from the blood in the systemic capillaries, carbon dioxide is taken up, and the uptake of carbon dioxide is associated with chemical reactions in the blood that decrease its affinity for oxygen. Hence more oxygen actually is given off at 46 mm. of mercury-carbon dioxide tension, which is the approximate level in tissues, than is indicated in the graph which shows the dissociation of hemoglobin in the presence of a carbon dioxide tension of 40 mm. of mercury such as is found in arterial blood.

Transport of Carbon Dioxide

When blood is exposed to carbon dioxide at a tension similar to that found in tissues (46 mm. of mercury), about 50 ml. of carbon dioxide is taken up per 100 ml. of blood. Only about 3 ml. of this is in simple solution in the plasma, and the remainder is chemically combined or *bound* carbon dioxide. About two-thirds of the bound carbon dioxide is contained in the blood plasma, and the other third is in the erythrocytes. The first reaction which occurs when carbon dioxide enters the blood is the combination with water to form carbonic acid.



The carbonic acid dissociates into H^+ and HCO_3^- ions. Since blood is slightly alkaline (pH 7.4), carbonic acid will react with base in the blood. As carbon dioxide enters the blood, the pH of the blood is reduced slightly toward neutrality, but the change in pH is slight, due to the presence of buffers which combine with considerable amounts of acid in the presence of only a minor increase in the hydrogen ion concentration. The reactions involved in the binding of carbon dioxide by the blood are complex. The important points are that carbon dioxide forms carbonic acid which combines with bases in the blood and that the pH of blood decreases toward neutrality as carbon dioxide is taken up. At the pH of

blood, hemoglobin and plasma proteins, as well as sodium and potassium, act as bases and serve as buffers to neutralize carbonic acid; furthermore, when hemoglobin gives up oxygen, it liberates base which becomes available to assist in carrying carbon dioxide. Thus, as the blood gives up oxygen to the tissues, its efficiency as a carrier of carbon dioxide is increased. The uptake of carbon dioxide by blood in the tissues and its liberation in the alveoli is accelerated by an enzyme, *carbonic anhydrase*, which promotes a more rapid development of an equilibrium, when water is exposed to carbon dioxide.

About eight to ten per cent of the CO_2 transported by the blood from the tissues is combined directly with hemoglobin. Thus, hemoglobin has both a direct and an indirect role (by giving up base) in the transport of CO_2 . This explains the fact that plasma from which the red blood cells have been separated will take up only a fraction of the amount of CO_2 that is absorbed by the same amount of plasma when the red cells are present.

Control of the pH of the blood. Arterial blood normally has a pH of 7.40 (plus or minus .05) and, due largely to the uptake of CO_2 , venous blood is slightly less alkaline. The constancy of the pH of the blood is maintained by three principal mechanisms. First, the blood contains combinations of substances which are known as buffer systems because they can react with considerable quantities of acid or base without undergoing large changes in pH. For example, sodium bicarbonate (NaHCO_3) which is found in the blood acts as a buffer, since it will react with a stronger acid such as HCl to produce NaCl and H_2CO_3 , and CO_2 can be given off from the blood. Second, the respiratory mechanism is sensitive to the CO_2 tension of the blood, and as a result a rise in CO_2 tension is counteracted by an increased level of breathing, so that the CO_2 level is prevented from rising greatly. Finally, the excretion of acid in the urine can vary within wide limits and this will occur to counteract any decrease in the pH of the blood. The renal mechanisms are discussed on page 383.

In diabetes, in which there is production of an excess of acid substances which must be excreted in the urine, and in kidney diseases, the renal acid-base regulating mechanism may be inadequate, and the pH of the blood may lie outside the normal range. The resulting condition is known as *acidosis* (decreased pH) or *alkalosis* (increased pH).

Chapter 26

REGULATION OF BREATHING

The carbon dioxide tension and oxygen tension of the blood are maintained within relatively constant ranges by the amount of ventilation of the pulmonary alveoli. In studying the mechanisms which regulate breathing, two quite different mechanisms are encountered; first, there are mechanisms for the control of the respiratory cycle, and second, there is the problem of regulation of the respiratory minute volume. The control of the amplitude and duration of inspiration is dependent mainly upon reflexes set up by distention of the lungs as inspiration proceeds. The adjustments of the pulmonary ventilation to the needs of the body, on the other hand, are accomplished largely through responses to changes in carbon dioxide tension, hydrogen ion concentration, and oxygen tension of the blood.

Effects of Oxygen and Carbon Dioxide

When one breathes back and forth into a large bag initially filled with air, the per cent of oxygen in the bag and in the subject's alveolar air decreases, and the carbon dioxide per cent increases. There results a progressive increase in both rate and depth of breathing, so that the respiratory minute volume may increase to several times the resting level. Similarly, if the trachea is obstructed so that the respiratory minute volume is decreased, changes in the composition of alveolar air like those seen in rebreathing occur, and the respiratory effort is greatly increased. In each of these conditions, two changes in the composition of alveolar air have occurred. Carbon dioxide tension in the bag and in alveolar air has increased, and oxygen tension has decreased; therefore, one would not know from this experiment alone which of these changes is concerned with the stimulation of breathing. In order to evaluate the effects of each

change, experiments must be designed so that each of the two changes is produced separately.

Oxygen deficit in the absence of a rise in carbon dioxide tension can be produced as follows. As before, the subject is allowed to breathe back and forth into a large bag filled with air, but a canister containing soda lime is placed close to the mask so that the carbon dioxide which is exhaled will be removed by combining with the soda lime. At the beginning of the experiment, the bag contains air which has an approximate composition of 21 per cent oxygen and 79 per cent inert gases. Since, in this experiment, the oxygen is being used up continuously, the per cent of oxygen in the bag decreases progressively, while the per cent of nitrogen increases. The changes in nitrogen tension, within atmospheric pressure ranges, do not affect breathing. Gas samples may be taken from the bag from time to time for analysis, and rate and depth of respiration are recorded continuously. Most subjects will begin to show mild stimulation of breathing when the oxygen content in the bag is between 15 to 18 per cent, at a barometric pressure around 760 mm. of mercury; the remainder begin to show stimulation in the range from 15 per cent down to 12 per cent. Thus, the experiment shows that when the carbon dioxide content of inspired air is kept constant, a lowering of the oxygen tension in the inspired air, and hence in the alveoli and arterial blood, elicits an increase in the amount of gas breathed per unit of time. At the same time, there is also an increase in the heart rate and cardiac output (page 231). The responses of the respiratory system and of the circulatory system obviously are compensatory in that they are such as to tend to maintain the oxygen supply to the tissues despite a decrease in the amount of oxygen delivered per unit of blood.

Although a decrease in oxygen tension, of the systemic arterial blood below the normal tension will cause an increase in RMV, an increase, as when 100 per cent oxygen is breathed at sea level, will not cause a decrease in breathing. The RMV is the same when a subject breathes oxygen at any per cent from 20 to 100, and the volumes per cent of oxygen in arterial blood is increased only slightly (page 292).

If a person rebreathes into a bag which originally contained pure oxygen, and if there is nothing present to take up the carbon dioxide which is being exhaled, the carbon dioxide tension in the bag will rapidly increase, and the RMV will increase proportionately. This occurs even though the oxygen tension in the bag is still far above the level in atmospheric air and hence above the level at which a compensatory increase

in breathing is elicited on the basis of lowered oxygen tension. Thus, it is evident that an increase in carbon dioxide tension will cause an increase in breathing.

If one voluntarily breathes rapidly and deeply, he lowers the carbon dioxide tension and increases the oxygen tension in the alveoli and in the arterial blood. When he stops the voluntary hyperventilation, he has no impulse to breathe for a fraction of a minute. Since this lack of breathing, or *apnea*, cannot be produced in a normal subject by excess oxygen, it must be attributed to the lack of carbon dioxide.

Control of Inspiration and Expiration

Inspiration is accomplished by coordinated activation of a number of muscles and simultaneous inhibition of their antagonists. At the same time, muscles in the nose, pharynx, and larynx which serve to increase the size of the air passages are activated. Expiration, although passive under some conditions, may involve powerful contractions of many muscles to accelerate the expulsion of air from the lungs. Coordinated activity of this type requires integrative mechanisms in the central nervous system. For a long time, it has been known that destruction of certain portions of the medulla oblongata will cause an animal to cease to breathe, whereas damage to large areas of the brain above this level do not cause failure of breathing. The portion of the medulla which is concerned with the integration of the breathing act is known as the *respiratory center*.

For many years, the mechanism of the rhythmic "discharge" of the respiratory center has been disputed, and the exact mechanism still is undetermined. To approach this problem, one needs to consider first some of the changes that suspend breathing. It has already been explained that there is no breathing for a brief period after hyperventilation, and that the apnea is attributable to lack of a sufficient carbon dioxide tension in the blood to elicit breathing. Another method of producing apnea is one which was demonstrated by Hering and Breuer in 1868. When the lungs are inflated by forcing air into them and the overinflation is maintained, breathing is temporarily suspended; however, after a brief period, breathing is resumed even though the inflation is maintained. Conversely, if the lungs are deflated by suction, breathing is stimulated. These effects on breathing which are produced by inflation or deflation of the lungs are eliminated if the vagus nerves are sectioned bilaterally. The role of the vagi is shown further by the fact that apnea occurs during stimulation

of the central end of the sectioned vagus nerve in experimental animals, and, after bilateral section of the vagi, there is a decrease in rate and an increase in depth of breathing. The cells in the respiratory center which are concerned with inspiration begin to "fire," largely on the basis of the direct stimulating effects of carbon dioxide (page 302); the muscles of

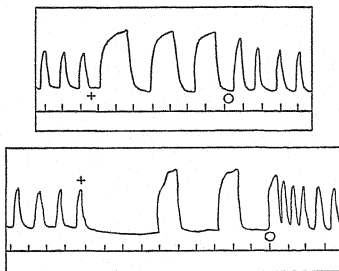


Figure 26-1. Record of contractions of separated slip of diaphragm of a rabbit to illustrate Hering-Breuer reflexes.

Upstroke is produced by contractions of the slip. *Above*, at + the trachea was occluded at the end of expiration so that the lungs could not be expanded during inspiratory efforts, and at O the obstruction was removed. *Below*, at + the trachea was occluded at the end of inspiration, and at O the obstruction was removed. (After H. Head, *J. Physiol.*, 10:1, 1889.)

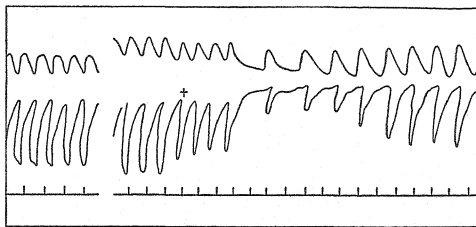


Figure 26-2. Effect on breathing produced by sectioning the vagus nerves.

On left, record shows fluctuation of intrathoracic pressure (*above*) and contractions of slip or rabbit's diaphragm (*below*) with both vagi intact. The left vagus was then frozen and slight slowing of respiration was produced as seen in the first part of the record following the break; then at + the other vagus nerve was frozen. (After Head, *J. Physiol.*, 10:1, 1889.)

inspiration are activated and expansion of the chest and lungs proceeds. As the lungs become distended, receptors in the lung substance are stimulated and impulses pass up by afferent fibers in the vagus nerves to the respiratory center in the medulla where they exert an inhibitory effect;

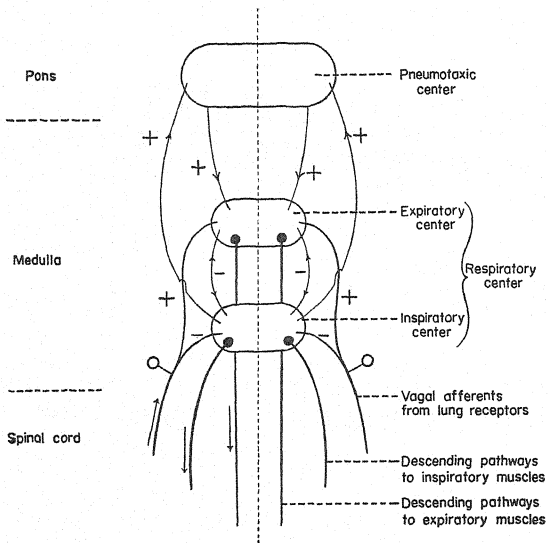


Figure 26-3. Diagram of neural mechanisms for the control of inspiration and expiration.

(From Youmans' *Basic Medical Physiology*.)

thus, inspiration is cut short. If the vagi have been sectioned so that this inhibitory influence is removed, the inspiration proceeds to a greater amplitude and the end result is deeper and slower breathing. The pathways for the Hering-Breuer reflexes are diagrammed in Figure 26-3.

Further understanding of the basis for rhythmic activation of the inspiratory muscles has been gained by considering the following experi-

ments which have been performed on anesthetized cats. Transection of the brain at the upper border of the medulla, which leaves intact the respiratory center and efferent pathways to the inspiratory musculature, does not cause cessation of breathing, and section of the vagi, as the only operative procedure, does not produce apnea; but when the two procedures are performed in the same animal, a sustained inspiration results.

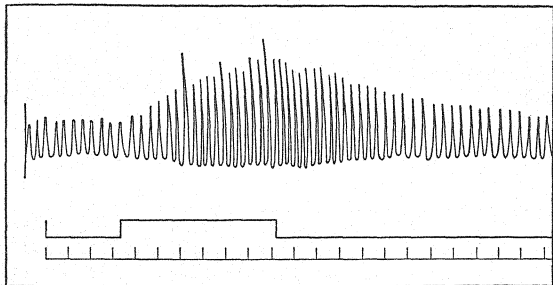


Figure 26-4. Effect of increase in CO_2 tension in the inspired air on the breathing of an anesthetized dog.

(From Youmans' *Basic Medical Physiology*.)

The cessation of breathing with the chest held in the inspiratory position is called *apneusis*. In some instances the animal shows occasional expiratory gasps rather than complete cessation of breathing. These results indicate that the cells in the inspiratory portion of the respiratory center are brought under inhibitory influences from two sources during inspiration. The first source of inhibition is the Hering-Breuer reflex mechanism. In the second place, as the inspiratory center discharges, impulses are sent up to a higher *pneumotaxic* center in the brain, located in the pons, and neurons in this center are activated to convey impulses back to the respiratory center.

Regulation of Pulmonary Ventilation

It is apparent that the amount of air breathed per minute needs to be correlated with the rate at which the body is using oxygen and producing carbon dioxide, hence it is not surprising to find that the body is equipped

with mechanisms by means of which either a rise in CO_2 tension or a decrease in oxygen tension of the arterial blood will stimulate breathing.

Mechanism for response to carbon dioxide. Under resting conditions, the responsiveness of the respiratory center to CO_2 and associated changes in hydrogen ion concentration is all important in determining the respiratory minute volume. The CO_2 tension of alveolar air and arterial blood is kept at about 40 mm. of mercury and the pH of the blood is maintained at about 7.4 largely through this mechanism. Any increase in CO_2 tension is counteracted by an increased RMV and any decrease causes depression of breathing until the normal level is restored. An increase in the CO_2 tension of the blood is accompanied by an increase in the acidity, hence it has been difficult to determine if each of these changes independently has a stimulant effect. There is evidence that CO_2 has a stimulant effect of itself and that the rise in acidity also has an excitatory effect which is added to the effect produced by the CO_2 .

Mechanism of response to oxygen lack. Some years ago, it was believed that a decrease in the oxygen tension in the blood had a stimulant action on the cells of the respiratory center. This is now known to be incorrect. A lowered oxygen tension does cause stimulation of breathing, but this response is elicited reflexly from chemoreceptors located in the carotid and aortic bodies. These bodies are small masses of tissue located in the bifurcation of the common carotid artery on each side and around the arch of the aorta (Figure 26-5). The chemoreceptors in the carotid and aortic bodies are innervated by the same cranial nerves (IX and X) which innervate the pressoreceptors of the carotid sinus and aortic arch. A decrease in O_2 tension causes an increase in the number of impulses conducted by the afferent nerves and these impulses have an excitatory influence on the respiratory center.

The chemoreceptors provide the only mechanism for producing any effective increase in respiratory minute volume in response to degrees of oxygen lack that can be tolerated for prolonged periods. No increase in breathing is elicited by a moderate decrease in oxygen content of the inspired air in animals which have had their chemoreceptor innervation destroyed. Severe oxygen lack may produce respiratory failure in such animals because of loss of responsiveness of the respiratory center without a phase of respiratory stimulation.

The carotid bodies also are stimulated by an increase in carbon dioxide tension to produce an increased ventilation rate if the rise is considerable. However, the respiratory center is stimulated long before this degree of

rise in carbon dioxide tension occurs; and, normally, the resulting increase in ventilation serves to prevent a rise in carbon dioxide tension to the level which would stimulate the chemoreceptors. The chemoreceptors also are sensitive to considerable increases in hydrogen ion concentration. In diseases characterized by severe acidosis, the decrease in pH in the chemoreceptors perhaps may be a factor in the stimulation of breathing.

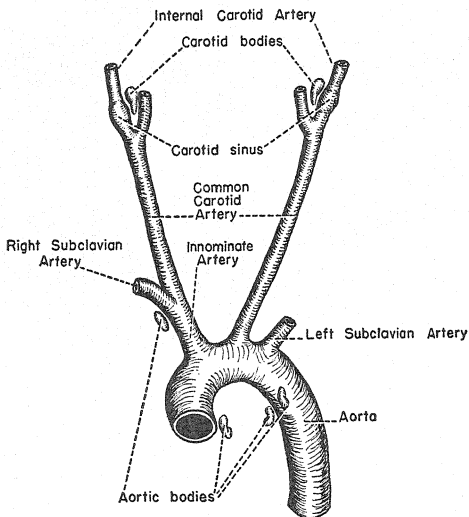


Figure 26-5. Locations of the carotid and aortic bodies.

(From Youmans' *Basic Medical Physiology*.)

In the normal person at rest at sea level, ventilation rate is maintained principally, or exclusively, by the action of the carbon dioxide tension and the hydrogen ion concentration on the respiratory center. The oxygen tension of the blood is at a level such that the role of the chemoreceptors is insignificant. At higher altitudes where the barometric pressure is lower, the oxygen tension of the inspired air is correspondingly lower

and the oxygen tension of alveolar air and arterial blood becomes lowered. In this case, breathing is reflexly stimulated from the chemoreceptors, and the alveolar carbon dioxide tension is decreased slightly as a result of the increased ventilation rate.

A sudden fall in pressure in the systemic arterial tree is associated with a marked stimulation of breathing, while a sudden rise in arterial blood pressure will cause apnea. The latter effect is illustrated in Figure 26-6. These responses are elicited reflexly from the carotid sinuses and aortic arch; they do not occur to any significant extent in animals having the pressure receptors denervated. However, it appears that denervation of the pressure receptors has no permanent effect on breathing.

Control of pulmonary ventilation during exercise. The carbon dioxide tension in the alveoli is elevated slightly in mild exercise; but in moderate or severe exercise it is decreased below the normal level, and there is no increase in carbon dioxide tension in the arterial blood. The oxygen tension of the arterial blood in exercise is not lowered sufficiently for this to be a factor of any importance in the stimulation of breathing. Therefore, factors other than changes in the tension of the respiratory gases in the arterial blood

must play a prominent role in the production of the increased ventilation rate during exercise. In severe exercise, the rate of production of acid metabolites exceeds their rate of removal by oxidation and the increased acidity may stimulate the respiratory center and possibly the chemoreceptors. However, it appears that the major part of the respiratory stimulation during exercise is accomplished (1) reflexly, by impulses

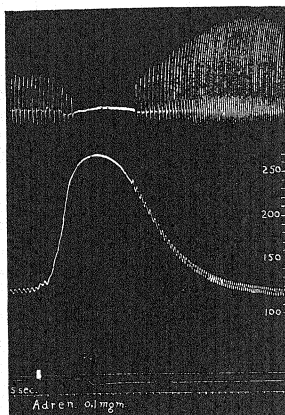


Figure 26-6. Reflex apnea produced by a rise in blood pressure following injection of epinephrine.

Upper record, respiration; lower record, arterial blood pressure. (Reproduced by permission from Bard, *Macleod's Physiology in Modern Medicine*. Copyright, 1941, by C. V. Mosby Co.)

carried over afferent nerves from receptors in the active muscles and joints and from receptors in the lungs and right side of the heart, and (2) by impulses reaching the respiratory center from the higher centers of the brain that are concerned with voluntary use of the skeletal musculature.

Anoxia

Anoxia or hypoxia refers to the development of a subnormal oxygen tension in tissues. The effects of lack of oxygen are quite variable depending upon the severity and duration of the anoxia and upon the tissues involved. The more active and specialized organs such as the heart and the central nervous system are more susceptible to anoxia than less specialized tissues such as the skin and connective tissues, which have a relatively low oxygen consumption. The irritable tissues may lose their ability to respond to stimuli as a result of anoxia and still maintain their viability, but if the anoxia is more severe or prolonged, viability also is lost and they do not recover even though the oxygen tension be restored. Anoxia may be produced by any one of three main types of defect described below.

Low oxygen-carrying capacity of the blood. In anemia, the blood may contain less than the normal amount of hemoglobin, and, consequently, the capacity for carrying oxygen is lowered. The blood flowing through the pulmonary capillaries equilibrates with a normal oxygen tension; therefore, the arterial blood has a normal oxygen tension. However, as the blood flows through the tissues, the usual amount of oxygen is removed and, since the total amount of oxygen in the blood is low, a greater per cent of the oxygen carried by the blood is removed. Thus, the active tissues cause the oxygen tension to be lowered to a level below normal.

In *carbon monoxide poisoning*, the gas forms a stable combination with hemoglobin and thus reduces the oxygen-carrying capacity of the blood just as if the hemoglobin content were low. Therefore, breathing carbon monoxide produces the anemic type of anoxia; the severity is in direct proportion to the amount of gas inhaled. Carbon monoxide does not stimulate the respiratory center, and the oxygen tension of the arterial blood is not lowered. Since the gas has no odor, unconsciousness and death may result without awareness of exposure to it.

Low oxygen tension in arterial blood. The oxygen tension of arterial blood is lowered if the alveolar oxygen tension is decreased or if the blood in the pulmonary capillaries cannot equilibrate with the alveolar air, or if, as in

certain congenital abnormalities of the circulatory system, the unoxygenated blood returning from the systemic veins becomes mixed with the oxygenated blood coming from the lungs. In this type of anoxia, the chemoreceptors in the carotid and aortic bodies are stimulated and there is an increased breathing effort which opposes the fall in oxygen tension.

When the oxygen tension of the blood is moderately lowered, as on ascent to altitude, there is an impairment of the higher functions of the brain. Usually, the subject is not aware of this; frequently, he must see comparisons of tests made at normal oxygen tensions and at altitude before being convinced that his efficiency is decreased. Therefore, it is necessary for aviators to begin breathing oxygen at a certain altitude rather than to depend upon experiencing the symptoms of oxygen lack. When an individual is subjected to low oxygen tension for prolonged periods, part of the acclimatization consists of an increase in the erythrocyte count in proportion to the decrease in oxygen tension in the blood (page 178).

A specific per cent of the hemoglobin present in the blood appears in the unoxygenated form at any given oxygen tension within the range from zero to 110 mm. of mercury. The *per cent* appearing in the reduced form can be read from the oxyhemoglobin dissociation curve (page 292); the *actual amount* of reduced hemoglobin present in a given sample of blood at a given oxygen tension is calculated by multiplying the per cent of reduced hemoglobin at that tension by the total amount of hemoglobin. If the amount of reduced hemoglobin present in the blood is sufficient, the skin appears bluish or *cyanotic*.

Decreased rate of blood flow. A third type of anoxia is that which is produced by a slower than normal rate of blood flow through the tissues. Even though blood with normal oxygen-carrying capacity arrives in a tissue carrying oxygen under a normal tension, if the flow through the capillary bed is slower than normal, a greater than normal amount of oxygen will be given up per unit of blood, and the tissue will function at a lower than normal oxygen tension.

Artificial Respiration

In an individual who has stopped breathing, it is essential that the oxygen tension of the blood be restored and maintained. Sometimes, carbon dioxide gas is administered to stimulate breathing in apneic subjects, but this may be ineffective, since the carbon dioxide tension already is elevated and there would be no apnea if the respiratory center were not in some degree refractory to carbon dioxide; furthermore, high concentrations of carbon dioxide have a depressant or anesthetic action on the respiratory center and may have ill effects on the circulatory system. The lack of sensitivity of the respiratory center to carbon dioxide usually is aggravated by a severe degree of anoxia of the center. Air or oxygen

may be administered by artificial respiration at a rate which does not lower the carbon dioxide tension below normal; and, if the respiratory center is still viable, shortly after the respiratory center becomes adequately oxygenated, it will regain its sensitivity to carbon dioxide. In the apneic individual, the object is to maintain the ventilation of the lungs so that the oxygen tension of the blood is adequate and a carbon dioxide deficit is not produced. This can be done by giving 100 per cent oxygen at a ventilation rate somewhat below or up to the normal level. When this is done, the oxygen tension will be considerably higher than normal and the carbon dioxide level of the blood will not be decreased. If the sensitivity of the respiratory center to carbon dioxide is regained, spontaneous breathing will be resumed.

Artificial respiration may be given by placing a close-fitting mask over the face and forcing a gas mixture into the lungs under *positive pressure*. In this case, one must be careful not to use high pressures, since there is the danger of rupture of an alveolus and the development of pneumothorax. Some devices for giving artificial respiration by the positive pressure method have a valve which allows the gas to escape if the pressure reaches a given level which cannot be exceeded safely.

Rhythmic application of pressure to the thorax is a more physiological method of producing ventilation than the positive pressure methods. It allows ventilation with air, and the dangers of positive pressure are avoided. It is useful when artificial respiration must be given for long periods. However, it is more difficult to maintain adequate ventilation by this method without the use of special apparatus, such as the Drinker respirator. By this device, commonly known as an "iron lung," positive and negative pressure may be rhythmically applied to the patient's body below the level of the neck.

Artificial respiration may be given for a short period by the mouth-to-mouth method. This is one of the most effective methods and may be used until special apparatus is obtained. Books dealing with First Aid may be consulted for the details concerning the actual procedures.

Chapter 27

MOTOR PROCESSES IN THE DIGESTIVE TRACT

The human organism is capable of using a great number of different organic compounds for food because these can be broken down in the digestive tract into relatively simple substances which are absorbable. In the preparation of substances for absorption, both mechanical and chemical processes are involved. The food is broken down by mechanical processes mainly in the mouth and stomach, and the chemical processes occur through the actions of enzymes contained in the juices produced by the digestive glands. Thus, the major processes which are included under the heading of digestion are: (1) motility in the various parts of the gastrointestinal tract, (2) mechanisms for causing the digestive glands to secrete at the proper time, (3) the actions of the digestive juices, or digestion proper, and (4) the absorption of the end products of digestion. Before considering these subjects, the general features of the anatomy of the digestive system will be described.

Physiological Anatomy

The digestive tract is a muscular tube composed of five major parts, the mouth and pharynx, esophagus, stomach, small intestine, and large intestine or colon (Figure 27-1). The small intestine is subdivided, consecutively, from the stomach into duodenum, jejunum, and ileum. The large intestine is composed of cecum and appendix, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum.

The walls of most of the parts of the digestive tube contain relatively thick layers of smooth muscle. In the middle and lower portions of the esophagus and the small intestine, the smooth muscle is arranged in outer longitudinal and inner circular layers. In man, the upper part of the esophagus is composed of striated muscle, while the lower portion contains

only smooth muscle. In dogs, the muscle layers of the entire esophagus are composed of striated muscle. The stomach has oblique layers of smooth muscle in addition to the other two coats. In the large intestine, the longitudinal layer consists of bands and does not form a complete coat. A cross

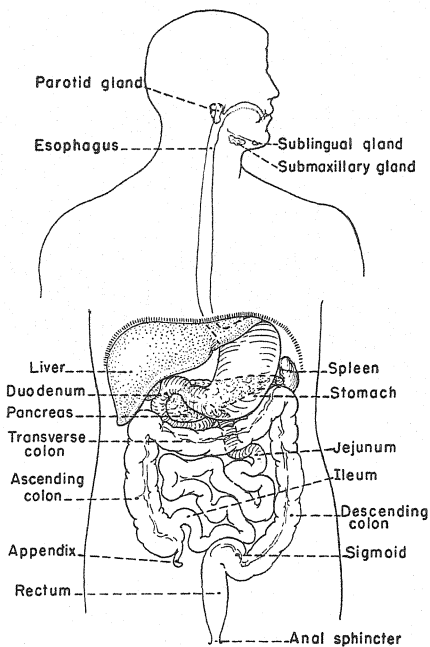


Figure 27-1. Parts of the digestive tract.

section of the small intestine shows, from the lumen outward (1) an epithelial or mucosal layer; (2) a layer of submucosa which contains a thin smooth muscle layer, the muscularis mucosa; (3) a ganglionated plexus of nerve fibers, the submucosal or Meissner's plexus; (4) an inner

circular layer of smooth muscle; (5) another ganglionated plexus called the myenteric or Auerbach's plexus; (6) an outer longitudinal layer of smooth muscle; and (7) the serosa, a tough fibrous layer of connective tissue covered with endothelium. The other parts of the digestive tube show modifications of this basic plan.

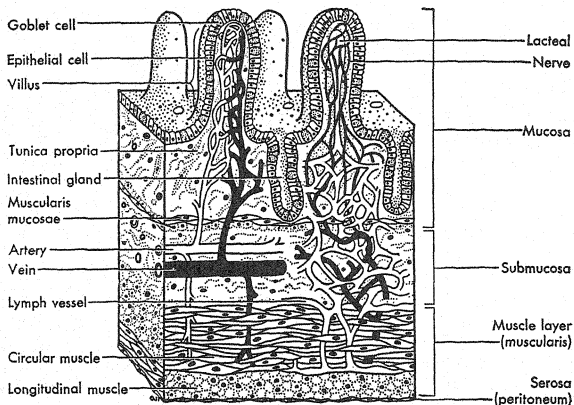


Figure 27-2. Wall of the small intestine.

Blood vessels only are shown in villus at left; lacteals and nerves only are shown in villus at right; however, all of these structures are present in each villus. (Reproduced by permission from Kimber, Gray, Stackpole, and Leavell, *Textbook of Anatomy and Physiology*. Copyright, 1961, by The Macmillan Company.)

The smooth muscle of the digestive tube is innervated by each of the two divisions of the autonomic nervous system and, as in other dually innervated effectors, these nerves are of two types, adrenergic and cholinergic (page 108). Most of the bowel receives its parasympathetic innervation from the vagus nerve; the colon is thought to receive some of its parasympathetic innervation from the vagus nerve and from the sacral part of the spinal cord. The stomach and small intestine are suspended from the body wall by means of the mesentery which contains the blood vessels, nerve fibers, and lymphatic channels.

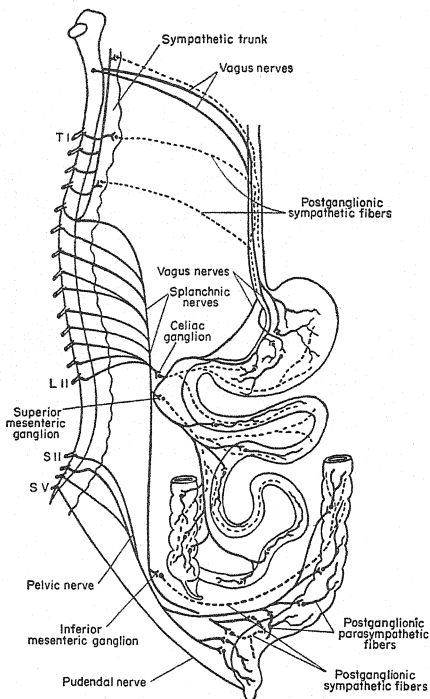


Figure 27-3. Diagram of the innervation of the gastrointestinal tract.

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Methods for Studying Gastrointestinal Motility

Many different methods have been used to study motor phenomena in the gastrointestinal tract. One of the most obvious methods is the direct observation of motility of the intestine of an anesthetized experimental animal that has had the abdomen opened. However, both the anesthetic agent and the surgery cause inhibition of gastrointestinal motility. The first use of X rays in medicine was by W. B. Cannon who, in 1896, observed the passage of a meal containing bismuth down the esophagus into the stomach and on into the small intestine. At the present time, radiological methods are used regularly to examine the various parts of the gastrointestinal tract when abnormalities of structure or motility are suspected. Of particular value in experimental studies is the determination of the length of time required for a meal to be emptied from the stomach. For example, the time required for a meal of standard composition to be emptied from the stomach can be determined under a standard set of conditions, and this can be repeated after giving a drug or after sectioning nerves to the stomach to see what effect is produced by these procedures. Also, the time required for the meal to traverse the small bowel can be recorded.

For the study of intestinal motility, much use has been made of fistulas in dogs. In the preparation of a Thiry or Thiry-Vella fistula, a segment of small intestine is brought out to open through the abdominal wall at the orad end of the segment or at both ends, and the continuity of the remainder of the bowel is re-established by suturing the remaining two free ends. Motility of the segments used for the fistulas can be recorded by the use of balloons connected with manometers or tambours or, in the case of the Thiry-Vella fistula, the rate of propulsion of a bolus from one end of the segment to the other can be determined. The fistulas, when properly prepared, do not interfere in any way with the health or longevity of the animals.

Types of Motility in the Digestive Tract

Several basic types of motility are observed in the gastrointestinal tract. If an object or bolus is placed in the lumen of the bowel, *peristalsis* usually develops. This is a ring of constriction which appears on the orad

side of the bolus and moves along the bowel. The propulsion of materials along the gastrointestinal tract is accomplished largely by peristalsis. Some parts of the digestive tract, for example, the jejunum, tend to show vigorous peristalsis as long as anything is present in the lumen, while other portions will show a lesser degree of peristalsis and hence will allow contents to remain for longer periods.

Non-propulsive types of motility in the bowel are referred to in general as *rhythmic* contractions. One type of rhythmic contraction lasts for a few seconds at the site of origin and then disappears. These contractions occur, first at one place, then another, along the small intestine and are known as segmenting contractions. Another type of rhythmic motility is called a pendular contraction. This appears to be a contraction of the longitudinal muscle over a section of bowel so that a shortening of the loop and, consequently, a sort of swaying motion is produced. The rhythmic contractions have a churning effect and thus help to mix the chyme with the digestive juices.

Finally, the smooth muscle of the digestive tract possesses *tonus*. It is found that when changes in pressure associated with motility are recorded, the minimum pressure reached at any time is above the atmospheric pressure level. A sustained pressure is exerted by the bowel and, since this pressure exceeds the intra-abdominal pressure, it is being produced by the wall of the intestine. There are two possibilities: either the intestine is resisting stretch simply through the elastic properties of the intestinal wall exclusive of any contraction of smooth muscle, or the pressure within the bowel is produced in part by muscular contraction. The latter has been demonstrated to be true. Variations in tonus of the bowel can be produced rapidly by injecting substances which increase or decrease the contraction of the muscle or by stimulating the efferent nerves to the bowel, while elastic properties of the intestinal wall cannot show such sudden marked changes. Thus, the gastrointestinal tract has tonus, in the sense of an active muscular resistance to stretch.

Role of the Nerves of the Digestive Tract

The nerves of the digestive tract include the extrinsic nerves and the intrinsic ganglionated plexuses. The intrinsic neurons of the intestinal wall which are innervated by the preganglionic vagal fibers apparently also receive connections from other intrinsic neurons, so that an anatomic

background for local intrinsic reflexes remains after elimination of both sets of extrinsic nerves.

The stomach, small intestine, and colon are able to carry out their motor functions in the absence of the extrinsic nerves, and all of the basic types of motility that are observed when the nerves are intact still remain after the extrinsic nerves are sectioned. The extrinsic nerves of the bowel are concerned with increasing or decreasing the level of motility and tonus in accordance with changing conditions in the bowel and in other parts of the body. However, in the upper part of the esophagus where the muscular component of the wall is of the striated type, its motility, including peristalsis, is dependent upon the extrinsic nerves. Peristalsis in the remainder of the digestive tract occurs in the absence of extrinsic nerves, but is dependent upon the intrinsic nerves. Peristalsis still can occur in isolated strips of intestine placed in oxygenated Locke's solution kept at body temperature, but it is prevented by substances which serve as local anesthetics or which prevent transmission of neural influences at synapses.

Rhythmic contractions of the intestine are present when the extrinsic nerves are destroyed and when the intrinsic plexuses are made nonfunctional either by local anesthetics or by agents which block synaptic transmission. In fact, isolated layers of intestinal smooth muscle when stripped away from the ganglionated plexuses may show rhythmic contractions when placed in suitable solutions.

The extrinsic innervation of the intestine is such that, in general, activation of the parasympathetic division, either artificially or under physiological conditions, promotes more rapid transit of contents through the bowel; the motility of the walls of the stomach, small bowel, and colon is increased and, at the same time, the sphincters are relaxed. The nerves concerned with these effects are cholinergic. The arterioles of the intestine are relaxed by cholinergic parasympathetic nerves so that the blood supply of the muscle and of the mucosa is increased. The sympathetic innervation of the bowel is predominately inhibitory, and the nerves concerned are adrenergic; activation of the sympathetic system or the presence of epinephrine in circulation causes decreased motility of the walls of the stomach and bowel and contraction of the sphincters. At the same time, the blood supply to the bowel tends to be decreased through vasoconstriction, and digestion and absorption are retarded.

The principal digestive glands receive an excitatory cholinergic innervation from the parasympathetic system. The digestive glands either

receive no sympathetic innervation or are not significantly influenced by this division of the autonomic system.

Chewing and Swallowing

The chewing of food, or mastication, serves to break down the ingested particles into a size sufficiently small to be swallowed, and the saliva which is mixed with the food serves as a lubricant. Chewing is a complex act which involves the coordinated activity of the muscles of the jaws, lips, cheeks, and tongue. Adequate sensory innervation of the tongue and of the mucosa of the lips and mouth also are essential. Six of the twelve cranial nerves contain either sensory or motor pathways which must be utilized in the process of mastication, hence ability to perform this act is impaired in a number of diseases in which the nervous or muscular system is involved.

The act of swallowing begins when a bolus is brought to the posterior part of the pharynx. This *first stage* of swallowing is under voluntary control. The *second stage* or the swallowing reflex occurs when the bolus comes in contact with the posterior pharyngeal wall or with the uvula. The reflex consists of a series of muscular responses which are such as to cause closure of the nasopharynx and larynx and to force the bolus into the esophagus. The larynx is moved upward and the epiglottis prevents entrance of food into the larynx which lies anterior to the esophagus. The remainder of the process of swallowing is the *third stage*. The wave of contraction set up in the pharyngeal musculature proceeds down the esophagus, and, as the wave approaches the lower end of the esophagus, the cardiac sphincter relaxes to permit the entrance of the bolus into the stomach.

The passage of liquids down the esophagus, if a person is standing, proceeds more rapidly than the peristaltic wave which is initiated by the swallowing reflex. In this case, if the liquid contains a material which is opaque to X rays, one may see that the swallowed fluid remains at the lower end of the esophagus just above the cardiac sphincter until the peristaltic wave catches up with it; then the contents are passed on into the stomach as a result of the relaxation of the sphincter and the push exerted by the peristaltic wave. If solid particles are swallowed, they may become lodged in the esophagus, and peristaltic waves may develop at the site of distention and serve to force the bolus on down the esophagus.

Motility of the Stomach

The human stomach as seen under the fluoroscope after the subject has swallowed a meal containing barium is shaped somewhat like the letter J. The parts of the stomach, illustrated in Figure 27-4, are the cardia, the fundus, the body, the antrum or pylorus, and the pyloric sphincter. The part of the duodenum which is adjacent to the pyloric sphincter is the duodenal cap.

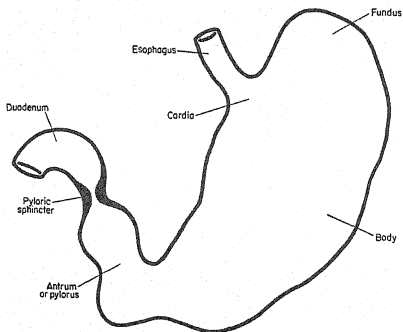


Figure 27-4. Outline of stomach as seen by fluoroscope.

As food is taken into the stomach, the gastric musculature undergoes an adjustment, or receptive relaxation, which makes possible a considerable increase in volume with only a slight elevation of the intragastric pressure. When the well-filled stomach is observed by the use of a fluoroscope, it may be seen that the fundus and body are relatively quiet. Constriction rings may develop at the junction of the body with the antrum and move down over the antrum. Usually, within a few minutes after taking a meal, one of these peristaltic waves will be seen to propel gastric contents through the pyloric sphincter into the duodenal cap. In addition to the peristaltic waves in the pyloric portion of the stomach, this region shows slow rhythmic fluctuations in tonus. The body of the full stomach remains relatively quiet; thus, it is seen that, as regards motor processes, the stomach is divided into two rather distinct parts; the upper

portion has principally a reservoir function, and the lower portion is concerned with churning and mixing the contents and with propulsive activity which promotes gastric emptying.

Emptying of the stomach. The fundamental mechanism for propulsion of contents from the stomach into the intestine, as for propulsion elsewhere in the bowel, is the peristaltic wave. Records have been obtained from the antrum, pyloric sphincter, and duodenal cap by the use of a series of three balloons, and it is evident in such records that a ring of constriction progresses downward over the three structures. Furthermore, the tonus of the pyloric sphincter decreases as the peristaltic wave approaches it, just as the cardiac sphincter relaxes when a peristaltic wave reaches the lower end of the esophagus. Some substances pass through the stomach rapidly, while other materials are retained in the stomach for longer periods. Considerable information has accumulated which provides explanations for the differences in rate of emptying of various substances from the stomach. Most of the factors which influence gastric emptying act in some way upon either the tonus or motility of the antrum or pyloric sphincter or duodenal cap. For example, if a solution having an acid reaction, in the range which develops in the stomach following ingestion of a meal, is applied to the mucosa of the antrum, the tonus of the pyloric sphincter decreases. However, if the same acidic solution is applied to the mucosa of the duodenal cap, the tonus of the pyloric sphincter increases. Thus, as a meal is acted upon in the stomach and as the acidity reaches a certain level, due to secretion of acid gastric juice, the pyloric sphincter will relax and the peristaltic waves will propel chyme into the duodenum. Then, the presence of this acidic chyme in the duodenum will elicit increased tonus of the pyloric sphincter until the acidity has been neutralized by the action of the alkaline bile and pancreatic juice. This is such an intriguing mechanism for regulation of gastric emptying that its relative importance probably has been overrated. There are some apparently normal individuals who produce little or no acid in their gastric juice, and in patients with pernicious anemia there is no production of acid, yet serious abnormalities of gastric emptying are not routinely present in persons having this disease.

It is well known that water or hypotonic solutions will pass through the stomach rapidly, while hypertonic solutions and particulate matter remain in the stomach for longer periods. The exact mechanism for the retention of hypertonic solutions is not clear, but a decrease in antral tonus or peristalsis or an increase in tonus of the pyloric sphincter most

likely occurs. Since gently stroking the pyloric mucosa with a blunt object will cause closure of the pyloric sphincter and relaxation of the antrum, this is probably a basis for retention of larger particles.

Meals including fat are retained in the stomach longer than meals containing only carbohydrate and protein. The mechanism for this has been shown to be hormonal. When the fat comes in contact with the mucosa of the upper duodenum, a hormone, known as *enterogastrone*, is produced in the mucosa and is liberated into the circulation to be carried to the stomach where it produces decreased motility. The same substance also inhibits secretion of gastric juice.

Conditions in the small intestine influence the rate of gastric emptying. Pressure in the duodenal cap not only directly opposes passage of contents from the stomach into the duodenum, but also elicits reflex inhibition of the stomach. The presence of contents in the lower ileum also has a restraining influence on gastric motility. When food is ingested, peristaltic waves traverse the entire small bowel and promote emptying of any ileal contents into the large bowel. This is known as the *gastroileal reflex*. The emptying of the ileum, allowing increased motility of the stomach, is called the *ileogastric reflex*. The latter response serves to illustrate how the extrinsic nerves of the bowel act to regulate motility of individual parts of the bowel on the basis of conditions in other parts.

Hunger and thirst. A person cannot ignore the need to ingest food and water for very long without experiencing characteristic unpleasant sensations which are familiar to everyone. Thirst seems to be due primarily to dryness of the mouth related to decreased secretion of saliva, but other less understood factors also appear to be concerned. Because of the sensation of thirst, the ingestion of at least the minimum amount of water needed for metabolism, perspiration, and excretion is insured providing water is available.

The sensation of hunger normally is related to characteristic contractions of the empty stomach. In numerous studies by W. B. Cannon and by A. J. Carlson, the motility of the stomach was recorded by means of balloons placed on the ends of catheters. In these experiments, the subject passed the balloon-tipped catheter down into his stomach and the other end of the catheter was connected with a suitable manometer. When such a record is taken shortly after the stomach has become empty, weak "tonus waves" are observed occurring at a rate of two or three per minute. After the stomach has been empty for a longer time, powerful contractions of the stomach appear periodically. Each of these contractions

lasts for a few seconds. If food is not taken, the contractions increase in frequency until they may occur in rapid succession or may become fused to produce periods of tetanic contraction of the stomach. The subject is not permitted to see the record and is instructed to make a signal (for example, by pressing a button which activates a circuit so that a mark is made on the drum of the kymograph) whenever he feels a "hunger pang."

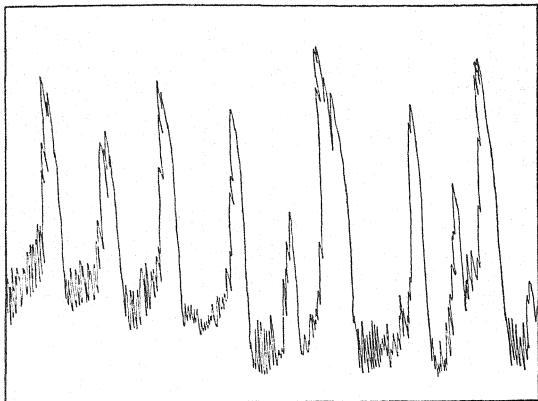


Figure 27-5. Gastric hunger contractions.

(Reproduced by permission, after Carlson, *Control of Hunger in Health and Disease*. Copyright, 1916, by the University of Chicago.)

In such experiments, it is found that the subject experiences hunger during each powerful gastric contraction, hence these waves are designated as hunger contractions. Hunger contractions stop when food is eaten or they may be depressed by injection of glucose intravenously. If no food is taken, the contractions tend to die away gradually after about thirty minutes to an hour and then start again after an hour or two. This is in accord with the observation that a fasting subject does not experience hunger continuously. After several days of fasting, hunger contractions may be infrequent or absent.

In general, the stomach in the normal individual becomes empty about one and one-half to three hours after a meal has been ingested, and

within another thirty minutes to an hour hunger develops. Many experiments have been performed to determine the mechanisms which underlie the production of the hunger contractions. One of the more enlightening experiments is the demonstration that an injection of insulin, which causes lowering of the blood glucose, will cause hunger contractions to appear; and intravenous injection of glucose will inhibit the insulin-induced hunger contractions. It has been established also that the stimulation of hunger contractions following injection of insulin can occur only if the vagal innervation of the stomach is intact. The blood glucose rises after a meal as a result of intestinal absorption, and may decrease sharply about three or four hours after a meal; hence an attractive hypothesis is that hunger contractions are induced under physiological conditions by a lowering of the blood sugar, and, thus, the individual is stimulated to take food which will result in a rise in blood sugar. If, however, a person who is hungry does not eat, glycogen in the liver will be converted into glucose and the blood sugar still will be prevented from undergoing a further decrease.

Hunger contractions are quite susceptible to influences from the sympathetic nervous system. An injection of epinephrine or stimulation of the sympathetic nerves will cause cessation of hunger contractions, hence it is not surprising that an individual who is experiencing a powerful emotion such as fear or rage ordinarily has no desire to eat. The motility of the full stomach and secretion of gastric juice also are inhibited in individuals experiencing acute pain or strong unpleasant emotions, so that a meal may remain undigested in the stomach for hours.

Whereas hunger has a physiological basis, *appetite* is a psychological phenomenon. It is a desire for food which is based on previous experiences with specific substances which are pleasant to the taste. Needless to say, one may experience appetite when the stomach is not empty and regardless of the level of the blood sugar.

The regulation of the total food intake over prolonged periods evidently is dependent upon the activity of hypothalamic centers (page 434).

Motility of the Small Intestine

The motor processes in the small intestine at a given site are related largely to the amount of contents. Ordinarily, there is little or no motility in the small bowel when it is empty. The bowel becomes active as a

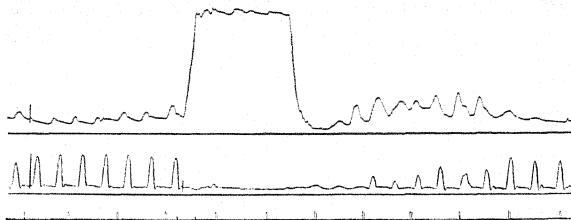


Figure 27-6. Reflex inhibition of intestinal motility elicited by intestinal distention.

A pressure record, using a balloon and mercury manometer, is taken from each of two intestinal segments in the form of fistulas. The pressure is suddenly increased in one of the segments (*above*) and rhythmic contractions in the other segment (*below*) are inhibited. Lowermost line shows time in five-second intervals. This type of response can be eliminated by sectioning the sympathetic pathways to the small intestine.

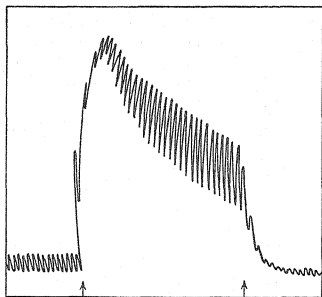


Figure 27-7. Effect of acetylcholine and atropine on intestinal motility.

This is a record of rhythmic contractions of a segment of rabbit jejunum suspended in oxygenated Locke's solution kept at body temperature. The lower end of the isolated segment is fixed and the upper end is connected with thread so as to pull a light lever. Addition of two drops of dilute acetylcholine solution (1 part in 10,000) to the Locke's solution bath caused the sudden shortening of the segment (upward movement of the writing point); then, a period followed during which tonus gradually decreased and amplitude of rhythmic contractions steadily increased. The sudden decrease in tonus and amplitude of contractions, seen at the right, was produced by the addition to the Locke's solution bath of two drops of a 0.1 per cent solution of atropine. The volume of solution in the bath was about 20 ml.

result of entrance of food into the stomach or when it receives contents, and the type of motility observed is related to the amount of filling. When the filling is slight or moderate and the pressure in the intestinal lumen is in the range of 5 to 15 cm. of water, rhythmic contractions are prominent and there is relatively little peristaltic activity, while at higher pressures there is considerable peristaltic as well as rhythmic activity. At pressures somewhat higher than 30 cm. of water, the intestine becomes distended and reflex inhibition is mediated by the extrinsic nerves. This effect is illustrated in Figure 27-6. The sympathetic system contains the efferent pathway for this response which is known as the *intestinointestinal inhibitory reflex*.

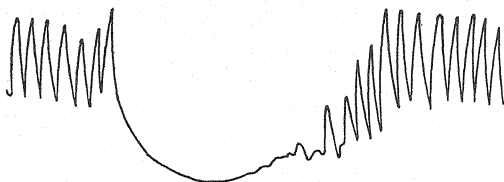


Figure 27-8. Effect of epinephrine on intestinal motility.

The record shows loss of rhythmic contractions and decrease in tonus which occurs when epinephrine comes in contact with intestinal smooth muscle.

All types of motility in the small intestine are stimulated by the cholinergic nerves and acetylcholine and are inhibited by adrenergic nerves and epinephrine. Inhibition of intestinal motility to the point of virtual paralysis is produced by severe distention or by irritation of the peritoneum such as occurs in *peritonitis*. The latter condition is an inflammation of the peritoneum or membrane which covers the abdominal organs and lines the abdominal cavity.

Vomiting

Vomiting is a mechanism for expelling food from the stomach. It involves coordinated action of smooth muscle in the upper small intestine, stomach, and esophagus and of striated muscle in the diaphragm, abdominal wall, pharynx, etc. Like respiration, vomiting is controlled by a rela-

tively small area, or vomiting center, in the medulla oblongata. This center may be influenced from higher neural centers or by afferent pathways, especially from the stomach and upper small intestine, or it may respond to substances reaching it by the blood.

Possibly, the first component of vomiting is the development of increased tonus in the duodenum. Next, the antrum is cut off from the body of the stomach by contraction at the *incisura angularis*. The feeling of nausea probably is related in part to these changes in gastric and intestinal motility, and salivation occurs concurrently with nausea. The body of the stomach, the cardiac sphincter, and esophagus become atonic, and minor adjustments occur in the muscles of the throat and larynx. Then, spasmodic simultaneous contractions of the diaphragm and abdominal muscles, which suddenly increase intra-abdominal pressure, provide the force for expelling the gastric contents. The gastric musculature itself plays a relatively unimportant role in vomiting.

Colonic Motility and Defecation

The principal functions of the colon are the storage of indigestible residue and the absorption of water. The colon shows strong contractions only intermittently. Stimulation of colonic motility commonly occurs just after eating, and the response is known as the *gastrocolic reflex*. Entrance of food into the stomach causes, through long reflexes, stimulation of the musculature of the colon, and it also causes emptying of ileal contents into the colon. Hence colonic pressure increases and contents may be transferred from the colon into the rectum. When the pressure in the rectum reaches approximately 40 to 50 mm. of mercury, the *defecation reflex* is elicited. This reflex is accompanied by voluntary contraction of the diaphragm and abdominal muscles to produce a marked increase in intra-abdominal pressure.

Constipation is a condition in which emptying of the large bowel is delayed. It is seldom due to any impairment of the neuromuscular mechanisms required for evacuation of the bowel. Constipation most frequently is caused by improper diet or by improper use of laxatives and cathartics. Habitual use of cathartics commonly leads to chronic constipation.

Diarrhea results when there is an abnormally rapid passage of contents through the small intestine and large intestine. Irritation of the mucosa of the intestine or the action of certain bacterial toxins may cause diarrhea,

or this condition may result from emotional disturbances. The ill effects of a prolonged period of diarrhea are related largely to the loss of water and salt from the body. The dehydration manifests itself in a decrease in the elasticity of the skin and a reduction in the interstitial fluid and blood volume. Individuals suffering from diseases which cause severe diarrhea are dramatically improved when physiological saline solution is given to them intravenously.

Chapter 28

DIGESTION AND ABSORPTION

Digestion, in a general sense, refers to all the processes occurring in the alimentary tract to transform food into a form which can be absorbed. In a stricter sense, digestion includes the chemical conversion of complex and, in some cases, insoluble substances into simple soluble substances which can be absorbed from the intestine. Digestion proper is accomplished through the actions of enzymes which are contained in the secretions that are liberated into the lumen of the digestive tract. The digestive juices are produced by glands which either empty into the tract by means of ducts or which are located in the epithelial lining of the stomach and small intestine. Each digestive gland is controlled by mechanisms which are such as to cause it to secrete at the time when the substrates upon which its enzymes can act are present in the part of the tract into which the secretion passes.

Not only do the digestive juices (except bile) contain one or more specific enzymes, but also the composition of each juice with regard to substances other than the enzymes is characteristic. For example, gastric juice is quite acid in reaction, and pancreatic juice and bile have a pH on the alkaline side. Appropriately, the enzymes in gastric juice work best in a solution having a pH of about 2.5 to 4, while the pancreatic enzymes are most active at a pH near the neutral point. It has been comparatively easy to study the actions of the digestive enzymes, since the digestive juices may be drained from the different portions of the gastrointestinal tract by means of tubes, and the enzymes exert their actions in the test tube if the chemical and physical conditions are suitable.

The factors which determine when secretion from digestive glands will occur are included in two major categories, humoral (or chemical) and neural. The secretory response of some glands is produced only by secretory nerves; the response of other glands is determined entirely by sub-

stances reaching them by the blood stream, and secretion from still other glands is controlled by both neural and humoral mechanisms.

Saliva

Saliva is produced by three glands, the submaxillary, sublingual, and parotid glands. The composition of saliva varies, particularly in mucus content, depending upon which gland produces it. The most important

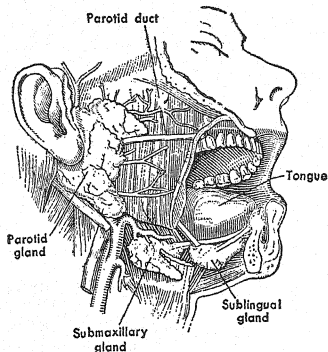


Figure 28-1. The salivary glands and their ducts.

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substances in saliva from the standpoint of digestive function are water, mucin, and the enzyme, *ptyalin*. The former substances serve to moisten and lubricate the food so that it may be swallowed, and ptyalin acts upon the digestible polysaccharides converting them into the disaccharide maltose.

Saliva has been a favorite digestive juice for studies in the student laboratory, since it can be readily collected simply by chewing some inert substance such as paraffin. The *pH* of saliva ranges around 6.8 and this is near the optimal for the action of ptyalin. Ptyalin acts slowly on raw starch, but rapidly hydrolyzes boiled starch into maltose. The more rapid digestion of boiled starch probably is due to the fact that the starch grain

is surrounded by an indigestible cellulose envelope which is disrupted by heating.

The relative amount of the total starch ingested which is digested by the action of ptyalin under most circumstances is probably small. The

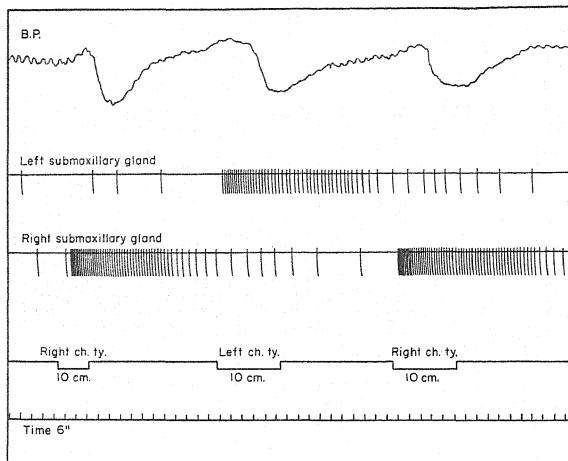


Figure 28-2. Increase in rate of production of saliva caused by stimulation of the secretory nerves to the submaxillary glands.

From above downward are shown (1) arterial blood pressure, (2) rate of production of drops of saliva from the duct of the left submaxillary gland, (3) similar drop record from the right submaxillary gland, (4) time of stimulation of the chorda tympani nerves which contain the secretory fibers to the submaxillary gland, (5) time in 6-second intervals. The cat has been given eserine which causes a slow flow of saliva and through its anticholinesterase action increases the response to stimulation of the cholinergic secretory fibers in the chorda tympani. (By permission, after Babkin, Alley, and Stavratsky, *Trans. Royal Soc. Can.*, 26:89, copyright 1932.)

food does not remain in the mouth for very long and ptyalin is virtually inactive at the pH to which it becomes exposed in the stomach. Most of the digestion of starch is accomplished in the small intestine as a result of the action of an enzyme in the pancreatic juice.

Nerve supply of the salivary glands. The salivary glands receive an efferent nerve supply from the VIIth and IXth cranial nerves (parasympathetic) and from the thoracolumbar system by fibers coming up through the cervical sympathetic trunk. The parasympathetic nerves are cholinergic. When the branch of the VIIth nerve supplying the submaxillary gland, the *chorda tympani*, is exposed and stimulated in experimental animals, or when choline derivatives are injected, a copious flow of saliva is produced, and the arterioles of the gland are relaxed so that the blood flow is increased. Stimulation of the cervical sympathetic trunk, on the other hand, causes vasoconstriction in the submaxillary gland and production of a few drops of viscous saliva.

The salivatory response to stimulation of the *chorda tympani* or to injection of acetylcholine is prevented readily by atropine. Atropine and related substances cause many of the cholinergically innervated visceral effector cells to become unresponsive to acetylcholine or to the effects normally produced by stimulation of their cholinergic nerve supply. It has been shown that atropine does not prevent production of acetylcholine by nerve fibers; it prevents the response of the effector cells to the acetylcholine, whether it is liberated at the nerve endings or reaches the cells by the blood stream.

Control of salivary secretion. The secretion of saliva under physiological conditions is controlled through the efferent nerves to the glands. No humoral control has been described. The secretion of saliva during eating is produced by simple reflexes and by conditioned responses (page 172). The simple reflexes are elicited from the taste buds as a result of chemical stimuli and by mechanical stimulation of receptors in the lingual and buccal mucosa. The conditioned responses can occur from seeing or smelling or thinking about palatable food. Conditioned responses and psychic bases for salivation, like the simple reflexes, utilize the efferent innervation of the salivary glands.

Gastric Juice

Methods for studying gastric secretion. Much of the knowledge concerning control of gastric secretion is derived from the studies by Pavlov, a famous Russian physiologist, who is well known also for his work on conditioned reflexes. Pavlov devised an operation to produce a gastric pouch in dogs as illustrated in Figure 28-3. In some dogs, he prepared, in

addition, an esophagostomy—an opening of the esophagus to the exterior in the neck—and in other animals he combined the pouch and a fistula into the intestine. In an animal with an esophagostomy, the food which is taken by mouth can be returned to a container fastened to the neck and in this way effects on gastric secretion produced by seeing, smelling, tasting, and chewing the food can be determined. This method is known as *sham feeding*. Also, food can be introduced directly into the esophagus so that the head, or cephalic, phase is by-passed. Between experiments,

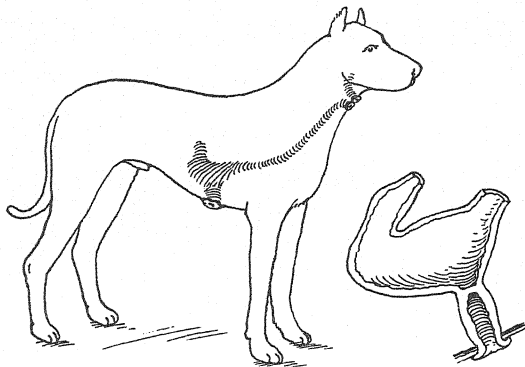


Figure 28-3. Sketch showing dog with esophagostomy and Pavlov pouch.

Details of the Pavlov pouch are shown in drawing on the right.

the two ends of the esophagus may be connected by a tube and thus permit maintenance of normal nutrition of the animal. Furthermore, when the studies are completed the continuity of the esophagus can be restored surgically. In an animal with an intestinal fistula, food can be introduced directly into the intestine so that stimuli to gastric secretion originating in structures anterior to the small intestine may be by-passed.

The gastric glands. The gastric glands are minute tubular units lying perpendicular to the surface of the mucosa. In a typical gland of the body of the stomach, three types of cells are seen: (1) chief cells of the neck or *mucous* cells, (2) chief cells of the body or *zymogenic* cells, and (3) *parietal* or border cells. These cells produce mucus, enzymes, and

hydrochloric acid respectively. In addition, the gastric juice contains an enzyme, *rennin*, which curdles milk, and there is a small amount of lipase. In the stomach of the adult, the digestive action of gastric juice is related almost entirely to the acid and pepsin content. The glands in the cardiac and pyloric portions of the stomach are different in structure than those found in the fundus.

Mechanisms for control of secretion. The control of secretion of gastric juice involves both neural and humoral mechanisms. The neural mechanisms cause the production of a juice that contains acid, mucus, and pepsin, while the humoral mechanisms cause the production of a considerably more acid juice containing relatively little mucus or enzymes.

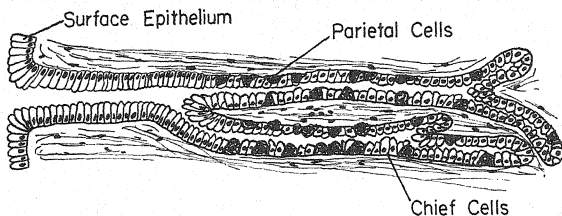


Figure 28-4. Structure of a gland in the mucosa of the body of the stomach.

Thus, it appears that all three types of cells found in the fundic glands are stimulated to secrete when their efferent nerve supply is activated, while perhaps only the parietal cells are sensitive to the humoral stimuli. Whether or not the other cells respond to humoral stimuli still is debatable. The gastric glands receive an excitatory cholinergic innervation from the vagus nerve. Direct stimulation of the vagus or injection of choline derivatives causes copious production of gastric juice which is rich in mucus, pepsin, and hydrochloric acid, and this action can be prevented by atropine.

The acid-secreting cells can be activated selectively by histamine. The juice produced following a subcutaneous injection of histamine has a pH between 0.9 and 1.5, while the gastric juice produced by vagal stimulation typically has a pH between 2.0 and 3.5. Histamine-stimulated gastric juice contains little or no pepsin, and this is especially true of the juice obtained in the last of a series of collection periods. Histamine can be extracted from the gastric mucosa in amounts greater than from other

portions of the gastrointestinal tract. Because of this finding and the fact that histamine is a potent stimulus to gastric secretion, it has been postulated that histamine has a physiological role in the stimulation of the gastric glands.

Secretion in response to feeding. The secretion of gastric juice in response to feeding is divided into phases on the basis of the *sources* of the influences. The *cephalic phase* of gastric secretion is the phase elicited by thinking about or by seeing, smelling, tasting, chewing, or swallowing food. This is the phase elicited by sham feeding. It is partly psychic or conditioned and partly reflex. The vagus nerve contains the efferent pathway for all of the influences on the gastric glands during the cephalic phase of gastric secretion. The response of the glands is depressed or prevented by atropinization and is eliminated in experimental animals by sectioning of the gastric branches of the vagus nerves.

The *gastric phase* of gastric secretion is that which results from the presence of food in the stomach. Both mechanical and chemical or humoral factors are concerned, but the humoral mechanisms are more important. When acid and certain other substances come in contact with the mucosa of the pylorus, a hormone, *gastrin*, is formed in the pyloric epithelium. This substance enters the blood and is returned by the systemic circuit to the glands of the gastric mucosa. Its action upon the gastric glands resembles that of histamine and differs from that of vagal stimulation.

The *intestinal phase* of gastric secretion is the phase elicited when chyme enters the intestine. It may be elicited by the introduction of a predigested meal directly into the small intestine through a fistulous opening. The amount of secretion produced on this basis is considerably less than that elicited by cephalic and gastric influences, and the mechanisms are not well defined. Theoretic possibilities are that a specific hormone is formed in the intestinal mucosa, or that substances absorbed from the intestine may be carried by the circulatory system to the gastric glands and there exert an excitatory action.

Digestion in the stomach. Most of the digestion in the stomach results from the activity of pepsin. This enzyme is present in the gland cells in the form of an inactive precursor, *pepsinogen*. After pepsinogen is secreted, it is converted into *pepsin* by the action of hydrochloric acid. The activation of pepsinogen occurs at a pH of 4.6 or below, and the pepsin is maximally active at pH 1.5 to 3.0.

Pepsin breaks peptide linkages of protein so that the protein ingested

is converted into intermediate products, *proteoses* and *peptones*. Only a small fraction of the total number of peptide linkages is broken by pepsin, and the splitting of the proteoses and peptones into amino acids is carried to completion in the small intestine. *Rennin* is an enzyme found in the gastric juice of infants; its presence in the gastric juice of adults is questioned. Rennin acts upon casein, the protein of milk, to convert it into paracasein which in turn is acted upon by calcium ions to produce an insoluble clot or coagulum. The clot tends to remain in the stomach and this permits continuation of digestion by the action of pepsin.

Peptic ulcer. The development of ulcers in the mucosa of the first part of the duodenum is relatively common. Less commonly, the gastric mucosa itself is involved. Usually, the ulcer crater can be visualized if the patient is given a meal containing barium. These lesions are known as peptic ulcers because they are produced by the action of the gastric juice. It is perhaps less surprising that ulcers occur than that they do not occur more frequently, since it would appear that the gastric juice should be capable of digesting the wall of the stomach itself. However, the mucus of the gastric juice seems to afford considerable protection, since, if it is kept washed away from a portion of the mucosa, ulcers are more apt to develop. Peptic ulcers can be produced experimentally by any procedure which causes a considerable and prolonged increase in secretion of acid gastric juice, and the ulcers heal if the secretion of gastric juice is depressed or if the juice is neutralized with alkali or removed. Certain emotions and nervous tension are associated in some individuals with neural stimulation of gastric secretion and development of peptic ulcers.

Pancreatic Juice

Control of secretion. The secretion of pancreatic juice is induced mainly by humoral mechanisms. When the acid gastric contents are emptied into the duodenum, a hormone, *secretin*, is produced in the intestinal mucosa and is carried by the circulatory system to the pancreas where it causes copious secretion of a juice which is alkaline and relatively poor in enzyme content. This is a self-regulating mechanism, since the pancreatic juice neutralizes the acid in the duodenum, thus decreasing the stimulus for further secretion of pancreatic juice. When there is further gastric emptying, the process is repeated, so that continued production of pancreatic juice is assured until the stomach is emptied.

The contact of chyme with the duodenal mucosa, besides causing production of secretin, apparently causes the formation of another hormone, *pancreozymin*, which is particularly potent in eliciting the secretion of

enzymes by the pancreatic cells. It is reported that these two substances have been prepared separately from the duodenal mucosa. Intermediate products of digestion, in the absence of acid, will cause production of pancreozymin.

As explained above, the composition of pancreatic juice varies with the type of stimulus. Juice obtained by vagal stimulation or by injection of choline derivatives is higher in protein and enzyme content and less alka-

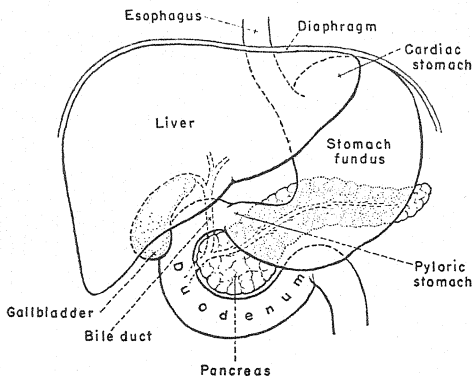


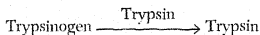
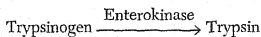
Figure 28-5. Diagram showing anatomical relations of the liver, pancreas, stomach, and duodenum.

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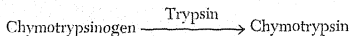
line than secretin-produced pancreatic juice. The pH ranges from 7 to 8; the alkali present is sodium bicarbonate. The pancreatic juice is the most important single digestive juice, since it contains enzymes concerned with the digestion of all three classes of foodstuffs.

Digestive actions of pancreatic juice. The precursor of a proteolytic enzyme, *trypsinogen*, is produced by pancreatic cells. Trypsinogen itself is inactive. When trypsinogen reaches the intestine, it is acted upon by an enzyme, *enterokinase*, in intestinal juice and *trypsin* is produced. Trypsin itself acts upon the remaining trypsinogen converting it into trypsin, so

that once a little trypsinogen is activated, soon all of it is activated. The reactions are as follows:



Another enzyme precursor, *chymotrypsinogen*, is present in pancreatic juice, and is converted to *chymotrypsin* through the action of trypsin.



Chymotrypsin clots milk and digests casein and gelatin, but, unlike trypsin, does not act upon polypeptides in general.

Trypsin is a mixture of several proteolytic enzymes which together act upon native protein or upon the intermediate products of pepsin activity

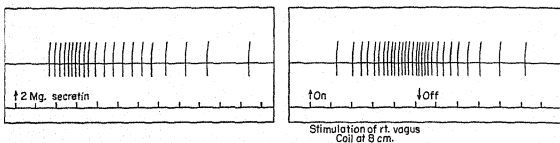


Figure 28-6. Drop record showing effect of injection of secretin (left) and of vagal stimulation (right) on secretion of pancreatic juice.

Each upstroke is produced by a drop of secretion falling from a cannula placed in the pancreatic duct of an anesthetized dog. Lower line shows time in 1-minute intervals. (By permission, after Thomas, *The External Secretion of the Pancreas*. Copyright, 1950, by Charles C Thomas Publishers.)

(proteoses, peptides, and polypeptides) to produce amino acids. However, trypsin does leave some polypeptides intact, and the digestion of these is completed by enzymes in the intestinal juice. As contents move along the small bowel, trypsin disappears; possibly it is itself digested and absorbed.

The pancreatic juice contains an enzyme, amylase or *amyllopsin*, which has the same actions as ptyalin; it converts starches, dextrins, and glycogen into maltose. In addition, the pancreatic juice contains small amounts of maltase which converts maltose into glucose.

Pancreatic juice exerts a powerful fat-splitting or lipolytic action, due to the presence of a *lipase* formerly known as steapsin. Pancreatic lipase

works best in a medium having a pH between 7 and 8, and its activity is increased four to five times in the presence of bile.

Intestinal Juice

Control of secretion. Intestinal juice is produced by small glands in the intestinal mucosa. The production of intestinal juice is elicited locally by the presence of contents in the lumen. Humoral mechanisms may play a small part in intestinal secretion; it has been claimed that a hormone, *enterocrinin*, is produced in the intestinal mucosa and is concerned with stimulating the intestinal glands. Mechanical stimuli are quite important. A profuse flow of intestinal juice can be induced simply by distending a segment of intestine with a balloon; or if a bolus of inert material such as paraffin or cotton is placed in the intestinal lumen, secretion is stimulated. The secretory response of an isolated intestinal segment is undiminished by section of the extrinsic nerves; therefore, secretion may be accomplished entirely by intrinsic mechanisms.

Actions of intestinal juice. The reaction of intestinal juice usually is slightly on the alkaline side. Freshly collected intestinal juice always contains enterokinase and amylase, and usually contains various peptidases (formerly known as *crepsin*), lactase, maltase, invertase, and lipase. The peptidases of intestinal juice cannot act upon native protein, proteoses, or peptones; they split polypeptides rapidly, at an optimal pH of 7.8, and convert them into amino acids. Lactase, maltase, and invertase or sucrase, split the disaccharides lactose, maltose, and sucrose respectively into simple sugars. The intestinal epithelium contains the enzymes found in intestinal juice; and, also, it usually contains enzymes which are not liberated, but which act upon certain substances after they have been absorbed into the cells.

Bile

The liver is a jack of many trades, hence its functions are considered in connection with several of the organ systems. The digestive functions of the liver are accomplished through the actions of the bile which it continuously secretes. The bile is carried to the gall bladder where it is stored and concentrated. Bile is emptied from the gall bladder through the common bile duct into the duodenum at the proper time to exert its

digestive actions. All substances which are absorbed into the blood from the intestine are carried to the liver by the portal vein and some of these substances such as bile salts and bile pigments are re-excreted into the bile, so that a continuous *enterohepatic* circulation of these substances is maintained.

Characteristics of bile. The principal constituents of bile are water, inorganic salts, bile salts, bile pigments, cholesterol, and lecithin. The bile which is produced by the liver differs considerably from that found in the gall bladder, since water and inorganic salts are absorbed from the bile in the gall bladder, so that bile salts, bile pigments, cholesterol, and lecithin become concentrated. Also, mucin is secreted by the epithelial cells lining the gall bladder.

The bile salts, sodium glycocholate and sodium taurocholate, from the standpoint of digestive functions are the most important constituents of bile. When the bile salts enter the small intestine they are absorbed into the capillaries of the intestinal mucosa and are brought back to the liver where they are excreted again. Under normal conditions, the bile salts circulate around in the *enterohepatic system*, and a minimum amount of synthesis of bile salts occurs. However, if a fistula of the bile duct is made so that the salts are drained to the exterior, synthesis of bile salts by the liver is stimulated.

The bile pigments, *bilirubin* and *biliverdin*, are produced when erythrocytes break down and release hemoglobin. Bilirubin is formed from hemoglobin by cells of the reticuloendothelial system which are found in large numbers in the liver, spleen, lymph nodes, and bone marrow. If severe hemolysis occurs, or if hemoglobin is injected intravenously, there is an increase in the amount of bile pigments. In the intestine, the bile pigments are converted into the pigment which is responsible for the color of feces. There is also an *enterohepatic* circulation of the bile pigments. In the presence of biliary obstruction, since bile pigments do not reach the intestine, the stools become less pigmented, or clay-colored.

Emptying of the gall bladder. The bile does not contain digestive enzymes but it influences the action of pancreatic lipase, it stimulates intestinal motility, and it is very important in promoting the absorption of fats (page 339). Since the bile is most important in influencing both digestion and absorption of fat, it is appropriate that the entrance of fat and egg yolk into the upper duodenum will cause emptying of the gall bladder. This is attributed to the formation in the intestinal mucosa of a substance, known as *cholecystokinin*, which is carried by the circulation to the

smooth muscle of the gall bladder. The cholecystokinin mechanism still can function when all of the extrinsic nerves of the gastrointestinal tract and liver have been sectioned.

Summary of digestion. Most meals contain all three of the major food-stuffs, carbohydrate, protein, and fat. In the mouth, some of the starch is converted into maltose. In the stomach, some of the protein is split into proteoses and peptones. The chyme which enters the small intestine ordinarily contains maltose, starch, protein, proteoses, peptones, and fat as well as any monosaccharides and disaccharides which were ingested. In the small intestine, starch is converted to maltose, and the maltose is split into glucose. Other disaccharides are split into monosaccharides. Protein, proteoses, and peptones are converted to amino acids in the small intestine, and fat is hydrolyzed into glycerol and fatty acids. Thus, it is seen that, although digestion of carbohydrate is initiated in the mouth and partial digestion of protein occurs in the stomach, all of the digestible substances may be acted upon in the small intestine through the influences of pancreatic juice, intestinal juice, and bile.

Sources and Actions of the Digestive Enzymes

COMPOUND DIGESTED	ENZYME	SOURCE	PRODUCT
Starch and dextrins	Ptyalin Amylopsin Amylase	Saliva Pancreatic juice Intestinal juice	Maltose Maltose Maltose
Maltose	Maltase Maltase	Pancreatic juice Intestinal juice	Glucose Glucose
Sucrose	Sucrase	Intestinal juice	Glucose and fructose
Lactose	Lactase	Intestinal juice	Glucose and galactose
Protein	Pepsin Trypsin	Gastric juice Pancreatic juice	Proteoses Proteoses Peptones Polypeptides
Proteoses Peptones Polypeptides Polypeptides	Trypsin Peptidases (erepsin)	Pancreatic juice Intestinal juice	Amino acids Amino acids
Fat	Lipase (steapsin)	Pancreatic juice Intestinal juice	Glycerol and fatty acids

Intestinal Absorption

Most of the absorption of the end products of digestion occurs in the small intestine. The surface area of the epithelium of the small intestine which is available for absorption is greatly increased by the presence of

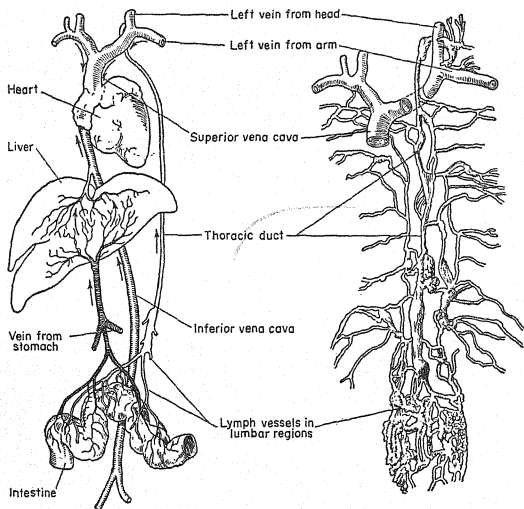


Figure 28-7. Blood vessels and lymph vessels into which end products of digestion are absorbed.

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folds of the mucosa, the *valvulae conniventes*, and microscopic finger-like projections, the *villi*. The villus may be considered as the functional unit for absorption. In the central portion of the villus, there is a lacteal that drains into larger lymph channels and these finally merge to form the lymph ducts in the intestinal mesentery. The ducts in the mesentery drain

into the chyle cistern which empties into the thoracic duct. The villus also is richly supplied with capillaries. Blood which drains from the capillary beds of the small intestine passes to the liver by the portal vein. Thus, absorbed materials may get into the general circulation either by the lymph ducts or by the portal vein.

The digestible carbohydrates are converted to simple sugars which can be absorbed. Glucose and galactose are removed from the intestinal lumen so much more rapidly than other sugars that, as described previously (page 31), a special mechanism for absorption of these compounds is indicated. During the absorption of a meal rich in carbohydrate, the blood in the portal vein shows an increase in glucose content, while the concentration of sugar in the thoracic duct changes only with changing concentrations in the arterial blood. This indicates that all of the absorbed glucose is carried by the blood from the intestine to the liver where some of the excess can be stored as glycogen.

Amino acids, the end products of protein digestion, likewise are absorbed into the capillaries of the villi and pass to the liver by the portal veins. This is indicated by the fact that the protein content of thoracic duct lymph is not increased during digestion, and ligation of the thoracic duct does not prevent the absorption of protein. Experimental animals and man have been adequately maintained on diets containing amino acids instead of native protein, hence neither protein as such nor any of the intermediate products of protein digestion, but only the amino acids derived from them, are required by the body.

A part of the fat that is ingested is hydrolyzed by lipases in the pancreatic and intestinal juice into glycerol and fatty acids. Some of the fat is emulsified so finely, through the action of bile salts, that it can pass through the intestinal wall without actual digestion. During absorption, fat appears in the epithelial cells in the form of minute droplets; from these droplets still smaller particles, called *chylomicrons*, make their way into the lacteals and thence into the thoracic duct and on into the blood stream.

Bacterial Action in the Bowel

The stomach contains relatively small numbers of bacteria; the number increases along the small intestine and becomes tremendous in the large bowel. Some of the products of bacterial action in the bowel are bene-

ficial if not actually essential. For example, vitamin K is produced by bacterial action in the intestine, and the amount supplied in the diet alone probably is inadequate in many individuals.

Fermentation of carbohydrates by bacterial action results in production of methane gas (CH_4), carbon dioxide, and organic acids. Absorption of these substances does not pose any problem. Putrefactive processes, on the other hand, result in the production of a number of substances which potentially are toxic. However, these substances are formed in small amounts and, after absorption, they are destroyed in the intestinal mucosa or in the liver so that they do not get into the systemic circulation. The absorption of toxic substances from the bowel does not constitute a medical problem except under extraordinary circumstances.

Chapter 29

TOTAL METABOLISM AND ENERGY EXCHANGE

With respect to energy exchanges, the human body can be compared with an engine such as the motor of an automobile. Certain substances which incorporate potential energy are fed into the engine; these interact to liberate energy, and waste substances are eliminated. In the case of the car motor, gasoline is the fuel which is burned, or oxidized, and in the case of the human body the organic foodstuffs are oxidized to obtain energy. In each case, heat is produced and must be given off to the surrounding air in order that the temperature of the machine does not progressively increase. The two machines are similar also in that a rather specific minimum amount of fuel must be burned to keep the engine running when it is performing no external work and additional fuel must be burned in proportion to the amount of external work done.

In the cells of the human body, many different chemical reactions are occurring simultaneously, and all of these reactions are included under the heading of *intermediary metabolism*. The term *total metabolism*, on the other hand, refers to the overall exchange of materials and energy; it represents the resultant of all of the numerous chemical reactions which occur in the body. To study total metabolism, one must consider what is put into the human machine and what is eliminated from it. The input of substances normally is through the digestive tract and the respiratory system, and the output is from these two systems and also from the skin and urinary tract.

Nutrition is the study which is concerned with the substances which must be included in the diet and with the amounts and proportions of these substances. The substances required are the three major classes of foodstuffs (page 14), and vitamins, minerals, and water. After absorption, these substances are used as fuel or they are built into body tissues or they enter into the regulation of various processes or chemical reactions. The end products of digestion of the major foodstuffs all can be

used as fuel. Certain of the amino acids and glycerol can be converted to glucose, and glucose can be converted to fat. Protein, being a nitrogen-containing compound, obviously cannot be produced from carbohydrate or fat; however, the protein in the diet may be spared from oxidation through the use of the other substances for fuel. The fact that interconversion and sparing can occur makes possible a wide variation in the proportion of carbohydrate, protein, and fat in the diet.

Energy Exchange

In the human body, as in animals in general, the exothermic reactions predominate over the endothermic reactions, hence the body is constantly producing heat. This accounts for the fact that the temperature of the body can be sustained well above that of the environment. Since the body is producing heat, while its temperature remains constant, the body must be losing heat at the same rate that it is being produced. This is true even though the rate of heat production varies greatly with changes in muscular activity and even though the environmental conditions change; therefore, it is evident that the body is equipped with mechanisms for regulating the rate at which it loses heat. These mechanisms are considered in another section (page 436). At this point, we are concerned with the methods of determining the *amount of heat produced*. For this purpose, two quite different methods can be used. The amount of heat given off by the body can be determined directly or, on the other hand, the amount of oxygen used under a standard set of conditions can be measured and from this the amount of heat produced can be calculated. These procedures are known as *direct calorimetry* and *indirect calorimetry* respectively.

The unit for measuring heat is the *calorie*. The word written with a small "c" refers to the amount of heat required to raise the temperature of one gram of water one degree centigrade under certain standardized conditions. One one-thousandth of a liter, or one milliliter (ml.), of water weighs one gram at ordinary temperatures and pressures. If one heats, for example, 100 ml. of water so as to increase its temperature 10° centigrade, the water has absorbed 1000 calories, or one Calorie, of heat. The large Calorie, distinguished from the small calorie by the capital "C," is equal to 1000 small calories. It is also known as a kilogram calorie.

The amount of heat which is given off as a result of oxidation of a specific amount of a substance can be determined by burning this sub-

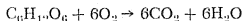
stance under conditions such that all of the heat evolved is absorbed by water. The device used for this purpose is known as a *bomb calorimeter*. Knowing the liters of water and the number of degrees increase in temperature, the number of calories liberated is calculated simply by multiplication. Substances such as carbohydrate and fat when catabolized in the body are completely burned; that is, they are oxidized to CO_2 and H_2O so that no carbon or hydrogen remains in a form that can be further oxidized. Hence the amount of heat liberated when these substances are burned in the body is the same as when they are burned in the bomb calorimeter. For carbohydrate, this figure is 4.1 Calories per gram, and for fat, it is 9.3 Calories per gram. The difference for the two compounds is largely a reflection of the fact that a molecule of fat contains a lesser proportion of oxygen than a molecule of carbohydrate, and, therefore, considerably more oxygen is required to oxidize a gram of fat than is needed to oxidize a gram of carbohydrate. When a gram of protein is catabolized in the body, 4.1 Calories are liberated. This is somewhat less heat than is liberated when protein is oxidized in a bomb calorimeter, and the difference is related to the fact that protein is not completely oxidized in the body; the $-\text{NH}_2$ group is split off and excreted from the body in the form of urea (page 374), whereas in the bomb calorimeter this part of the molecule also is oxidized.

Direct calorimetry. For direct calorimetry, the subject is placed in a small insulated room, the temperature of which is kept down to a constant comfortable level by water which is piped through it. The heat given off by the subject warms the water. The data recorded include the temperature of the water flowing in, the temperature of the water flowing out, and the total amount of water flowing through per unit of time. From these data, the number of calories absorbed by the water to keep the room temperature constant is calculated, and this is equal to the amount of heat given off by the subject. Although this method is simple in theory, in practice it is complicated and requires expensive equipment. Hence it is useful only for research.

Indirect calorimetry. In indirect calorimetry, the heat production is not measured, but is calculated mainly from information concerning the amount of oxygen used and carbon dioxide produced. This is possible, first because a *certain amount of heat is liberated per liter of oxygen used* in oxidizing each of the major foodstuffs, and second because there is a *specific ratio between the amount of carbon dioxide liberated and the amount of oxygen used* to oxidize each of the major foodstuffs. The

former figure is known as the *calorific value of a liter of oxygen* and the latter ratio, expressed as CO_2/O_2 , is called the *respiratory quotient*.

The respiratory quotient can be calculated from the balanced chemical equations. For example, six-gram molecular weights of oxygen are required to oxidize one-gram molecular weight of glucose to carbon dioxide and water; and the amount of carbon dioxide produced is six-gram molecular weights.



When subjected to the same set of conditions, one-gram molecular weight of a gas contains the same number of molecules and occupies the same volume as one-gram molecular weight of any other gas (page 24). Therefore, the volume of carbon dioxide produced when glucose is burned is the same as the volume of oxygen used; the ratio is 1/1, which gives a respiratory quotient of 1. This value for the respiratory quotient is obtained for all of the carbohydrates. Molecules of protein and fat contain a lower ratio of oxygen to carbon than is found in carbohydrate; therefore, they require relatively more oxygen from extra-molecular sources when they are oxidized, so that the ratio of carbon dioxide produced to oxygen consumed is less than one. The respiratory quotient for fat is 0.71 and for protein it is 0.80.

To determine heat production by the indirect method, one must know the amount of oxygen used by the subject and the proportion of carbohydrate, protein, and fat being burned. In order to obtain the information concerning the amounts of each substance being catabolized, the CO_2 production and amount of nitrogenous wastes excreted by the kidney must be measured in addition to the O_2 consumption. In actual practice, however, usually, one is interested in the heat production under a standard set of conditions or, in other words, the *basal metabolic rate* (BMR), in order to compare the energy metabolism in a given case with the average for normal subjects. Under basal conditions, it has been found that the proportion of the three classes of foodstuffs being burned is quite constant. The respiratory quotient under these conditions is constant at 0.82 and the calorific value of a liter of oxygen is 4.82 Calories. Thus, the determination of heat production by the indirect method under basal conditions is done simply by measuring the amount of oxygen used per unit of time (in liters) and multiplying this by 4.82.

Basal Metabolic Rate

Determination of basal metabolic rate is done extensively as a clinical laboratory test. The subject is instructed to eat a light, protein-poor supper

on the day before the test. On the morning of the test, he fasts or eats a light breakfast containing mostly carbohydrate. When the subject arrives at the laboratory, he is allowed to rest in the recumbent position for thirty minutes; then, he is connected with the mouthpiece of the device which

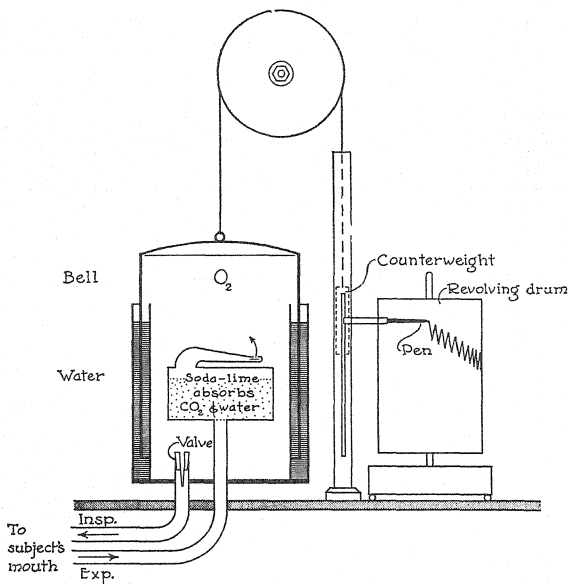


Figure 29-1. Apparatus for determining rate of oxygen consumption.

(Reproduced by permission from Amberson and Smith, *Outline of Physiology*. Copyright, 1939, by The Williams & Wilkins Co.)

measures the oxygen consumption (Figure 29-1). The spirometer contains oxygen and a chemical (soda lime) which removes the carbon dioxide which is exhaled. As the subject inhales and exhales, the bell of the spirometer is moved up and down and these excursions are recorded on a revolving drum. On each exhalation, the bell rises to a lower position

than the preceding level because oxygen is used up and the carbon dioxide which is exhaled is removed by the soda lime. A record of about eight minutes duration is obtained; then, the paper is removed from the drum and a straight line is drawn through the peaks which mark the expiratory position at the end of each breath. From this straight line, the decrease in oxygen in the spirometer during each minute can be read. It is necessary, of course, that the observed oxygen volume be corrected to standard conditions before multiplying by the figure for the calorific value of a liter of oxygen.

Basal metabolic rate determinations have been made on large numbers of normal subjects. It has been found that age, sex, and size are the more important factors which influence the BMR. In order to have a figure which takes size into consideration, the BMR is expressed in terms of surface area, and the figure for this is derived from the height and weight of the subject. BMR is slightly higher in males than in females of the same surface area and decreases slowly with aging in both sexes. The mean heat production for a young adult male under basal conditions is about 39 Calories per hour per square meter. The BMR is expressed as the per cent above or below the mean for normals of the same age group and sex. Thus, a BMR of +10 indicates that the individual has a basal rate of heat production which is ten per cent greater than the average for normals of his age and sex. However, a person may be normal without being average. For example, although there is an average height, no one would claim that a person is not normal if he is moderately shorter or taller than this. The same principle applies in the case of the BMR; the BMR for over 90 per cent of normal persons lies within the range from -20 to +20. Marked deviations such as +40 or higher or -30 or lower always are associated with disease if the test and calculations have been properly performed.

The Caloric Requirement

As stated above, an average young adult male under basal conditions produces 39 Calories per hour per square meter. If this person is of average size, his surface area will be about 1.75 square meters. Therefore, in 24 hours he would produce $1.75 \times 24 \times 39$ Calories, or 1638 Calories, even though engaged in no physical exertion. The total energy require-

ment of the individual is determined by his basal metabolism and by consumption beyond the basal. The latter is due mainly to skeletal muscular activity. For moderately active men, the energy requirement is about 3000 Calories per day and for moderately active women about 2500 Calories. If for any reason, not enough food is eaten to provide for the caloric requirement of the body, some of the carbohydrate, protein, or fat of the body will be burned as fuel and the body weight will correspondingly decrease.

The number of calories obtainable from any food or diet can be estimated if one knows the weight of each substance present. The weight of each substance in grams is multiplied by the calories produced by that substance per gram. For example, if a diet contains 100 gm. of protein, 90 gm. of fat, and 400 gm. of carbohydrate, it will provide 2878 Calories:

Protein	100 grams @ 4.1 Cal./gm. =	410 Cal.
Fat	90 grams @ 9.2 Cal./gm. =	828 Cal.
Carbohydrate	400 grams @ 4.1 Cal./gm. =	1640 Cal.
Total caloric value		2878 Cal.

Tables are available which give the approximate amounts of carbohydrate, protein, and fat and the caloric values for each of the common foods. Ordinarily, the protein intake should not be less than 70 gm. per day, and if it is below 50 gm. per day, more nitrogen is excreted from the body than is ingested. This signifies that protein of the body tissues is being catabolized. In the fasting or chronically undernourished individual, the basal heat production decreases to a greater degree than the decrease in either weight or surface area. Nitrogen excretion continues at a fairly constant level in the fasting subject, and the amount present in the urine indicates that he is catabolizing about 50 gm. of his body protein daily. The weight loss of the various tissues and organs during fasting is disproportionate; it is most in fat, spleen, liver, and muscles and least in the heart and central nervous system.

Whenever the amount of food eaten is more than enough to provide for growth or repair and for the energy requirement of the body, the deposition of fat occurs. This is known as simple, or exogenous, obesity. In endogenous obesity, likewise, the food intake is in excess of that needed by the individual, but the food requirement is lowered or the desire for food is increased as a result of some disturbance in neural or endocrine functions.

Specific Dynamic Action

The metabolic rate during the absorption of a meal and for a variable period afterwards, depending on the type of meal, is greater than under otherwise comparable conditions in the fasting subject. This is the basis for giving consideration to the content of the two meals preceding the determination of the BMR. The stimulatory influence, or *specific dynamic action*, of protein is several times as great as that of carbohydrate or of fat. Specific dynamic action may be expressed as the excess amount of calories liberated beyond the basal level which occurs following the ingestion of foods. As an example, if protein sufficient, on oxidation, to produce 100 calories is eaten, the total heat production above the previous basal level which will occur is 30 calories; the figures for carbohydrate and fat are 6 calories and 4 calories respectively.

The specific dynamic action of protein is produced after absorption, and hence is attributable to amino acids. Only certain amino acids produce a striking effect on metabolic rate, namely, tyrosine, phenylalanine, glycine, and alanine; leucine and glutamic acid have smaller effects, and the other amino acids (see table, page 350) exert little or no specific dynamic action. The specific dynamic action of amino acids probably is related to the energy expenditure associated with the removal of amino groups and the formation of urea (page 351), since it is not seen in protein-deficient animals in which the amino acids are not catabolized, but are synthesized into protein.

Chapter 30

INTERMEDIARY METABOLISM

The chemical reactions into which the end products of digestion enter after absorption are extremely complex. To study these in any detail, a background in organic chemistry, physical chemistry, and enzymology is required. This subject makes up a considerable part of advanced courses in biochemistry. In this chapter, only the broad general aspects of the subject are considered.

Essential Amino Acids and Complete Proteins

Protein which is taken into the body is broken down by digestive enzymes into amino acids which are absorbed from the intestine. Although the body does not require any specific protein as food, it does require considerable amounts of certain amino acids. By means of numerous experiments, it has been shown that laboratory animals require these amino acids for normal rate of growth, while immature, and for maintenance of normal conditions in adult life. The other amino acids need not be included in the diet, since those which are needed can be synthesized in the body from other substances. The nutritional importance of the amino acids is summarized in the table. The amino acids in the right-hand column are *essential*, but can be replaced by the corresponding amino acid in the middle column. Those in the left-hand column are not essential.

Some proteins contain all of the essential amino acids in amounts sufficient to maintain animals in normal condition when any one of them is included as the only protein in the diet (Figure 30-1). Such a protein is known as a *complete protein* to distinguish it from the incomplete proteins which lack one or more of the essential amino acids. The albumins of eggs, milk (casein), and lean meat are complete proteins, while

Nutritional Importance of Amino Acids

NON-ESSENTIAL	ESSENTIAL	
Glycine	<i>Irreplaceable</i>	<i>Replaceable</i>
Alanine	Threonine	
Serine	Valine	
nor-Leucine	Leucine	
Aspartic acid	iso-Leucine	
Glutamic acid	Methionine	Cysteine: cystine
Proline	Phenylalanine	Tyrosine
Hydroxyproline	Histidine	
	Tryptophane	
	Lysine	
	Arginine *	

* Arginine apparently can be synthesized by the growing animal, but it cannot be synthesized fast enough to permit the optimal rate of growth; therefore, it is included with the essential amino acids.

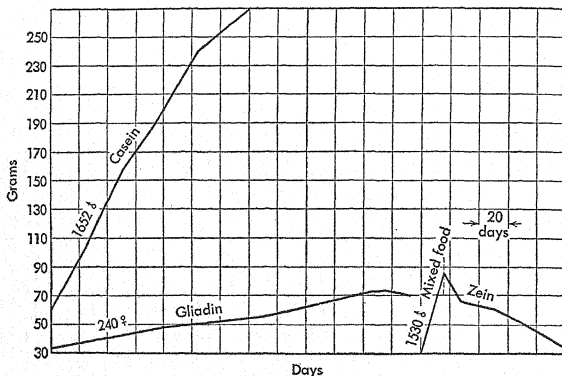


Figure 30-1. Growth curves of rats maintained on diets containing a single protein.

Note poor growth on gliadin, a protein which is deficient in lysine. Excellent growth is obtained with casein as the only protein fed. On the right, it is shown that excellent growth is obtained with mixed food containing several proteins, but weight loss occurs after changing to a diet containing no protein other than zein which is deficient in lysine and tryptophane. (L. B. Mendel, *Harvey Lectures*, 10:111, copyright 1914-15.)

zein and gliadin are examples of incomplete proteins, since they lack one or two essential amino acids. If zein is the only protein being fed to immature laboratory animals, growth is retarded and will not proceed at the normal rate unless both tryptophane and lysine are added to the diet. This is illustrated in Figure 30-2.

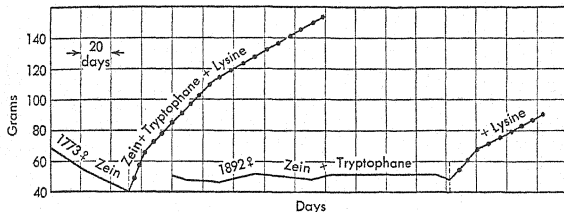


Figure 30-2. Effect on rat growth produced by adding the essential amino acids, tryptophane and lysine, to a diet containing no protein other than zein.

On the left, it is shown that the rat was losing weight on zein alone and gained weight rapidly when the two amino acids were added to the diet. On the right, it is shown that body weight was being maintained on zein plus tryptophane and weight gain occurred when lysine also was added. (L. B. Mendel, *Harvey Lectures*, 10:111, copyright 1914-15.)

General Metabolism of Amino Acids

The amino acids are used in the synthesis of body protein which forms the framework of the tissues. Also, the enzymes and some of the hormones are composed of protein. Some of the essential amino acids are incorporated in certain of these substances (pages 396 and 403). The amino acids which are not needed for synthesis of protein in the body are deaminated, in which case the amino group is split off and eventually is excreted in the form of urea. The deaminated residue of the amino acid may be oxidized to provide energy, and in the case of some of the amino acids it can be converted into glucose. The sources and uses of the amino acids are shown in Figure 30-3.

Nitrogen balance. When the body is growing, the intake of nitrogen exceeds that which is lost in the excreta. This is known as a positive nitrogen balance. As already explained, in the fasting individual the excretion

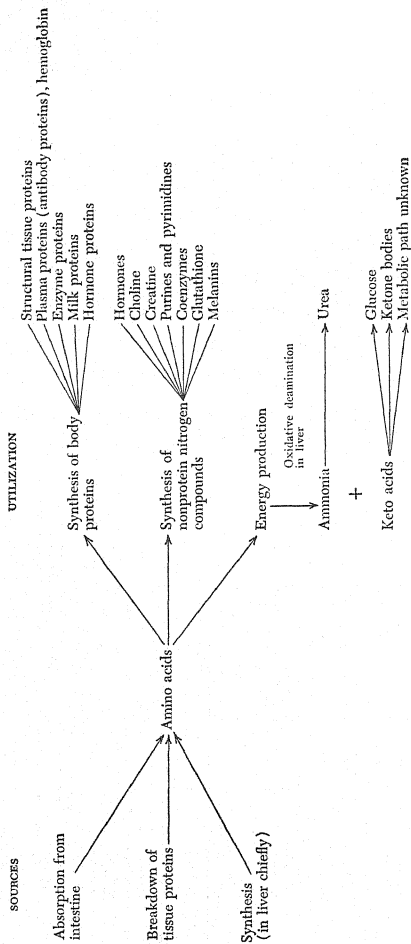
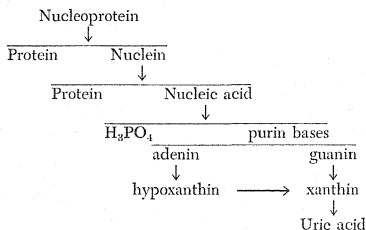


Figure 30-3. Sources and uses of amino acids.

of nitrogen continues in the absence of intake, hence such a person has a negative nitrogen balance. In a normal adult on an adequate diet, there is an equilibrium such that the intake of nitrogen is similar to the loss.

Nitrogen wastes. The nitrogen-containing end products of protein metabolism are excreted mainly in the urine. For an individual on an ordinary diet, 80-90 per cent of the urinary nitrogen is in the form of *urea*. The absolute amount excreted daily is 9-12 gm. of nitrogen or 20-30 gm. of urea. The amount of urea nitrogen excreted per 24 hours is, in general, an index of the amount of food protein catabolized during that period. Normally, the blood contains from 8-15 mg. of urea per 100 ml., and this level mounts rapidly if, for any reason, kidney function is seriously impaired. Most of the urinary nitrogen other than that present in the form of urea is in *creatine* and *creatinine*. *Ammonia* also appears in the urine in small amounts. Its production by the kidney is discussed on page 383. *Uric acid*, another nitrogenous waste, is the end product of the metabolism of a class of conjugated proteins, *nucleoproteins*. These are compounds of simple basic proteins, *protamines* and *histones* with *nucleic acid*. As diagrammed below, the protein is split off from the nucleic acid, and the breakdown of nucleic acids results in the formation of purine bases which are modified slightly to form the uric acid which appears in the urine.

Steps in Breakdown of Nucleoprotein



Metabolism of Fats

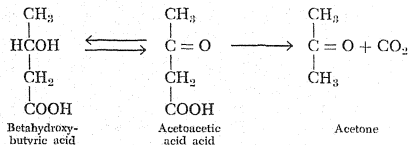
Although carbohydrate and fat can replace each other in the diet within wide limits, in experimental animals normal growth and well-being are not possible in the complete absence of dietary fat. The fat-soluble vita-

mins are not effective in curing the symptoms produced by fat-deficient diets. Characteristic deficiencies in rats are alleviated by the administration of linoleic acid. On the basis of experiments of this type, it is now considered that linoleic acid ($C_{17}H_{31}COOH$), linolenic acid ($C_{17}H_{29}COOH$), and arachidonic acid ($C_{19}H_{31}COOH$) are *essential fatty acids*.

The end products of fat digestion are glycerol and fatty acids. The glycerol can be converted into glucose, and either glucose or fatty acids can be oxidized to provide energy. If food intake is in excess of that needed to meet the energy requirements of the body, the fatty acids and glycerol are reconstituted into body fat.

Oxidation of fatty acids. The fatty acid molecule is a long carbon chain (page 17), and the best evidence at present indicates that oxidation of this chain occurs at alternate carbon atoms. Thus, many two-carbon units are formed as intermediate products as the fatty acid is split. These two-carbon units then enter into further chemical reactions which result finally in their complete oxidation. Among these reactions is the condensation of pairs of two-carbon units into *ketone* bodies.

Ketone bodies. The ketone bodies are *betahydroxybutyric acid*, *acetoacetic acid*, and *acetone*. It may be seen by reference to the formulas below that the first two of these compounds contain four carbon atoms in a straight chain. As stated above, they are believed to be produced by condensation of pairs of the two-carbon units derived from the breakdown of the fatty acid chain. Acetone is derived from acetoacetic acid when CO_2 is split out of the carboxyl group.



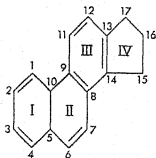
The liver appears to be the chief site of formation and interconversion of the ketone bodies.

Ketone bodies are produced in considerable amounts only under unusual circumstances. This occurs, for example, in serious degree in *diabetes mellitus*, a disease caused by lack of the hormone, insulin, which is produced by the pancreas. Insulin, as will be explained in the latter part

of this chapter, is concerned primarily with glucose metabolism; however, when glucose cannot be utilized normally, the production of ketone bodies by the liver is stimulated. According to one view, ketones are liberated when the supply of glucose is low (starvation or low carbohydrate diet) or cannot be utilized (*diabetes mellitus*) in order to supply the tissues with an emergency fuel. Under these circumstances, the rate of production of ketone bodies exceeds the rate of utilization; the blood level increases and the substances are excreted in the urine. Since the four-carbon ketone bodies are acids, they combine with base in the body and base is excreted along with them. Ultimately, if this process continues, a severe acidosis is produced (page 294), and it is the acidosis which is most dangerous in the diabetic patient.

Lipotropic compounds. Certain compounds are capable of counteracting the deposition of fat in the liver in animals being fed a high-fat diet. These are known as *lipotropic* compounds. *Choline* and *methionine*, an essential amino acid, are included in this group; and a substance, known as *lipocaic*, which is extracted from raw pancreas, has a similar effect.

Sterols. One of the classes of simple lipids includes esters of fatty acids with cholesterol. Cholesterol is one of a class of substances, known as steroids, which have a four-ring structure, as shown below.



The sterols are steroids which have an hydroxyl group attached to carbon atom number 3. Other steroids which are important in human physiology are the D vitamins, the bile salts, the sex hormones, and hormones of the adrenal cortex.

Metabolism of Carbohydrates

All of the digestible carbohydrates are hydrolyzed to simple sugars in the digestive tract and these are absorbed from the small intestine. The most important of the simple sugars and the one regularly found in the

blood is glucose. Some of the glucose is carried to the liver by the portal vein after absorption and there it is converted into *glycogen*, the storage form for carbohydrate in the body. Glycogen stores also are found in muscle and in the central nervous system. Since glycogen is insoluble and since a large number of glucose molecules are joined to form a single molecule of glycogen, the osmotic effect of the glucose is largely prevented when the conversion to glycogen occurs. In the postabsorptive state, although glucose is being used continuously as fuel, the blood level is maintained within a certain normal range by the conversion of liver glycogen into glucose. This is known as *glycogenolysis*. During prolonged fasting, the glycogen stores become depleted and the body must begin to use up fat and protein. The production of glucose in the body from protein is known as *gluconeogenesis*. It will be recalled that a number of the amino acids can be converted to glucose, while others cannot.

Blood glucose level and its regulation. In the fasting subject, blood glucose level is maintained at a relatively constant level. This is another example of the principle of *homeostasis*, namely, that the body is equipped with mechanisms which serve to maintain the *status quo*. During fasting, the body has the problem of keeping up the blood glucose in the presence of continued utilization, and glycogenolysis or gluconeogenesis occurs at a rate just sufficient to do this. During absorption of glucose, the body is stimulated to convert glucose to glycogen and thus the rise in blood sugar is counteracted. The ability of the body to take up glucose from the blood can be determined by injecting a standard amount of glucose intravenously and analyzing blood samples withdrawn at certain intervals after the injection. The graph obtained is known as a *glucose tolerance curve* (Figure 30-4). If the rise in blood sugar is greater and longer than normal, the individual has a decreased glucose tolerance. Such a result occurs typically in patients with *diabetes mellitus*.

The removal of glucose from the blood normally occurs mainly through oxidation or as a result of its conversion to glycogen. However, under some circumstances, glucose is excreted by the kidney. At the usual blood sugar levels, no glucose appears in the urine, but when the level reaches 160 to 170 mg. per 100 ml. the *renal threshold* is exceeded and glucose is excreted. The renal threshold for glucose occasionally is exceeded in normal persons for a short time after meals rich in starch and sugar, and this is especially true if a person has not been in the habit of eating much carbohydrate. The presence of sugar in the urine under these conditions is known as *alimentary glycosuria*.

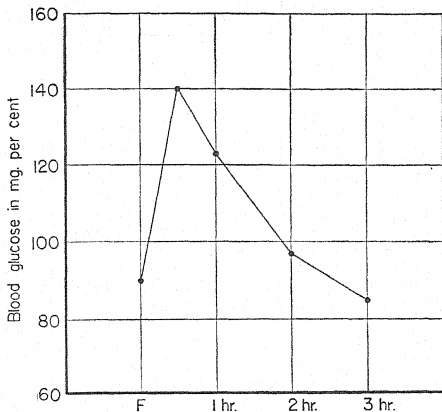


Figure 30-4. Oral glucose tolerance curve.

Changes in level of glucose in the blood in a normal subject following ingestion of a standard amount of glucose. (From Youmans' *Basic Medical Physiology*.)

Role of the pancreas. The pancreas contains the islets of Langerhans which are the site of production of the hormone *insulin* (page 406). A rise in the glucose level of the blood such as occurs after eating elicits the liberation of insulin and this in turn causes the conversion of glucose to glycogen by the liver and other structures. The action of insulin in lowering blood sugar is evident from several types of experiment. In the first place, if the pancreas is removed from an experimental animal, the fasting blood sugar level becomes elevated to a range where glycosuria is more or less constant. The condition produced closely resembles *diabetes mellitus*. Second, the injection of glucose into animals having the pancreas removed produces a much greater rise in blood sugar than it does in normals. In other words, such animals show a decreased glucose tolerance. Finally, injection of insulin is followed by a fall in blood sugar which is greater, the larger the dose. By injections of insulin, the blood sugar can be lowered to levels far below the normal and produce characteristic symptoms. Low blood sugar is known as *hypoglycemia* and high blood sugar is *hyperglycemia*.

Role of epinephrine. The normal range for the blood sugar is about 80 to 120 mg. per 100 ml. of blood. When the blood sugar decreases severely, for example, to below 40 mg. per 100 ml., following injection of a large dose of insulin, epinephrine is liberated from the adrenal medullae (page 402) and this hormone promotes the conversion of glycogen to glucose. If epinephrine itself is injected into either the hypoglycemic or the normal individual, it will produce a considerable rise in the blood sugar, or when epinephrine is liberated in the body, on the basis of a stimulus other than hypoglycemia, it causes hyperglycemia which may be of a degree sufficient to produce glycosuria.

In experimental animals, for example, rabbits, if a dose of insulin is given which is so large that it cannot be counteracted by the epinephrine liberated by the animal in response to hypoglycemia, convulsions occur when the blood sugar gets to very low levels. The skeletal muscular activity is associated with breakdown of glycogen to glucose and of glucose to pyruvic acid, some of which is resynthesized to glucose, and the blood sugar usually rises during the convulsion. Then the convulsion ceases, perhaps due to the rise in blood sugar, but the blood sugar decreases again and the process is repeated until the animal dies or gradually recovers, depending upon the dose of insulin given. The insulin-induced convulsions in experimental animals can be relieved dramatically by intravenous injection of glucose, or they can be relieved temporarily by injection of epinephrine.

Role of the pituitary gland, adrenal cortex, and thyroid gland. Three endocrine glands in addition to the pancreas and the adrenal medulla have important influences upon carbohydrate metabolism. These are the anterior lobe of the pituitary body, the adrenal cortex, and the thyroid gland.

After removal of the anterior pituitary (hypophysectomy) in experimental animals, absorption of glucose from the intestine is decreased and carbohydrate stores are rapidly depleted. The removal of the pancreas produces a hyperglycemia and glycosuria; subsequent removal of the anterior lobe of the pituitary alleviates the experimental diabetes in that it causes the blood sugar to decrease toward the normal range. A dose of insulin about one-tenth that required to affect the glucose level of the blood of a normal animal will cause severe hypoglycemia and convulsions in the animals having no anterior pituitary. The hypersensitivity to insulin can be abolished by giving anterior pituitary extract, or in normal animals insulin insensitivity can be produced. *Injection of anterior*

pituitary extracts into normal animals has profound effects on carbohydrate metabolism; hyperglycemia and glycosuria are produced in dogs, and the effects of injecting insulin are counteracted.

The *role of the adrenal cortex* in carbohydrate metabolism is demonstrated mainly by effects of removal of the adrenal glands and effects of injection of extracts of the adrenal cortex. After *adrenalectomy*, there is depletion of carbohydrate levels in liver, muscle, and body fluids, and the fasting animal excretes less nitrogen than the amount excreted by the normal fasting animal. Also, diabetes of pancreatic origin is alleviated. The *injection of extracts of adrenal cortex* into either adrenalectomized or normal animals causes an increase in liver glycogen and in the blood sugar, while muscle glycogen remains unchanged. It is concluded that glucose is produced from protein, or, in other words, *gluconeogenesis is stimulated*. The increased excretion of nitrogen in the urine is derived from the amino groups which are removed from amino acids prior to conversion of the latter to glucose. In general, adrenal cortical extracts and active crystallin steroids isolated from the adrenal cortex produce, on injection, a hyperglycemia and glycosuria and aggravate the diabetes produced by removal of the pancreas.

Since the level of activity of the adrenal cortex is controlled by the *adrenocorticotrophic hormone* of the anterior pituitary (page 391), some of the effects of hypophysectomy and of injection of anterior pituitary extracts are exerted indirectly through their effects on the adrenal cortex. The effects of the anterior pituitary on gluconeogenesis evidently are exerted through the adrenal cortex, while the effects on rate of utilization of glucose possibly are directly on the tissues.

The *thyroid gland* produces a hormone that has a stimulating effect on metabolism. Basal metabolic rate is increased to as much as 50 per cent above the mean level. Tissue protein catabolism is increased; there is an acceleration of the utilization of fats, and liver glycogen is depleted. The tolerance to glucose taken by mouth is decreased; probably because of an increased rate of absorption of glucose. It appears that the alterations produced by an excess or deficiency of thyroid hormone are related mainly to the change in rate of metabolism.

It is evident that the maintenance of the blood sugar level within the normal range is accomplished mainly through the interactions of several hormones. Thus, the level is kept constant in spite of huge variations both in the amount of carbohydrate ingested and in the amounts used in metabolic processes.

Oxidation of glucose. When glucose is oxidized in the body, energy is liberated and CO_2 and H_2O are produced as waste products. The reaction is written as the reverse of that which designates photosynthesis (page 19). However, this equation is simply a summary of the result of a complex series of chemical reactions. The breakdown of glucose in the animal organism is known as *glycolysis*, which literally means dissolution of glucose. At an early stage in glycolysis, the six-carbon chain is split into a three-carbon chain and pyruvic acid is formed. This compound can enter into a cyclic series of reactions that can be viewed as a sort of mill into which acetoacetic acid and acetate from breakdown of fats and of certain amino acids and pyruvic acid from breakdown of other amino acids also are fed, and energy CO_2 and H_2O are fed out. Thus, there is a catabolic "pool" into which intermediary compounds from the breakdown of each of the end products of digestion can be poured as needed. The pool can be fed by whichever of the end products of digestion are available until the energy requirement of the body is met.

Chapter 31

VITAMINS AND MINERALS

The fact that the body needs specific organic substances other than carbohydrate, protein, and fat became evident several decades ago in experiments in which animals were fed simplified diets. It was found that animals develop certain abnormalities when given only the three major foodstuffs in pure form along with adequate amounts of inorganic salts and water. It was then determined what foods must be added to the simple diet to relieve the deficiencies or to protect against the development of the abnormal condition. Once a "protective" food was found, it could be divided into fractions to determine the chemical nature of the substances responsible for the beneficial effect of the food. The "protective" substances are known as *vitamins*. Vitamins differ from other essential dietary constituents such as some of the amino acids and fatty acids in that they are not used for building tissue nor are they catabolized to supply energy. They are concerned primarily with the *regulation* of metabolic processes, and in this respect they resemble the hormones which in turn differ from vitamins in that they are produced in the body. From the standpoint of nutrition, the important vitamins are those which, under any circumstances, may not be included in the diet in adequate amounts. Although the list of vitamins is still growing, it is unlikely that additional vitamins in this category will be found.

The vitamins are subdivided into the *fat-soluble* group, which includes vitamins A, D, E, and K, and the *water-soluble* group, which includes vitamin C and the vitamin B complex.

Fat-Soluble Vitamins

Vitamin A. Vitamin A is a complex organic compound with the empirical formula $C_{20}H_{20}OH$. Vitamin A may be supplied as such in the diet or

it may be produced from carotene, which is called *provitamin A*. The carotene molecule if split in half would yield two molecules of vitamin A. Carotene is a part of the pigment in most green and yellow plants; therefore, leafy vegetables and carrots are rich sources. Carotene is affected little by heat, hence cooking does not destroy it. Certain fish-liver oils, butter, eggs, and cheese are rich sources of vitamin A. Bile salts are needed in the intestinal absorption of vitamin A and the other fat-soluble vitamins.

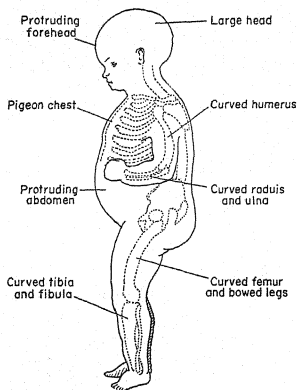


Figure 31-1. Diagram showing the principal skeletal changes seen in infantile rickets.

(Reproduced by permission from Best and Taylor, *The Living Body*. Copyright, 1952, by Henry Holt and Co., New York.)

Deficiency of vitamin A produces inability to see in dim light, or *night blindness* (page 156). Severe deficiency in animals produces characteristic changes of the tear glands so that drying of the eyes, or *xerophthalmia*, occurs, and ulceration and infection of the cornea may result. Mild deficiency produces dryness and scaliness of the skin; and in some cases of severe vitamin A deficiency in man, a roughening of the skin, *follicular hyperkeratosis*, is produced.

The minimum daily requirement of vitamin A is about 5000 units for both children and adults.

Vitamin D. Vitamin D is a sterol which is present in large amounts in fish-liver oils. Also, the skin of the human body contains sterols which are converted into vitamin D by irradiation with ultraviolet light (one of the wave lengths present in sunlight); therefore, the dietary intake of vitamin D can be reduced or eliminated if there is adequate exposure of the skin either to sunlight or to artificially produced ultraviolet light.

Deficiency of vitamin D causes alterations in the metabolism of calcium and phosphorus (page 371). The alterations are manifested in children as *rickets* and in adults as *osteomalacia*. In rickets, the inorganic salts are not deposited in bone sufficiently rapidly. Among the deformities which develop are bowlegs, knock-knees, enlargement of the ends of bones at the joints, and bead-like swellings on the ribs at the junction of the bone with the cartilage connecting it to the sternum. Vitamin D deficiency also may cause an increased incidence of dental caries. In osteomalacia, calcium and phosphorus are lost from bone. The softness of the bones which results leads to characteristic deformities. The calcium level of the blood may be decreased so that *tetany* develops.

Vitamin E. There are several forms of vitamin E, the alpha-, beta-, and gamma-tocopherols. Vitamin E is found in certain plant oils, in most green-leaved plants, and in meat, butter, eggs, and fish-liver oils. Also, vitamin E activity is shown by other compounds which are structurally unrelated to the tocopherols.

In both male and female rats, a deficiency of vitamin E causes damage to the reproductive system. If the female becomes pregnant, the embryo dies and is resorbed. In some species of experimental animals, vitamin E is necessary for normal development of the skeletal musculature. In the human, it is not yet demonstrated that the vitamin is necessary or that a deficiency ever occurs.

Vitamin K. There are several naphtha-quinone derivatives that have vitamin K activity. Vitamin K is present in green vegetables, tomatoes, cheese, egg yolk, and liver, and it is synthesized by bacteria in the digestive tract.

Vitamin K is not absorbed from the intestine in adequate amounts in the absence of bile; therefore, the characteristic changes produced by deficiency of this vitamin occur when there is obstruction of the biliary passages. Lack of vitamin K in the adult seldom occurs from deficient intake; it is usually related either to lack of absorption, secondary to

lack of bile in the intestine, or to reduction in the number of vitamin K-producing bacteria in the intestine following the administration of certain drugs.

Vitamin K deficiency results in a tendency to bleed profusely from minor wounds, and the clotting time of the blood is found to be greatly prolonged (page 185). The increased clotting time is related to a decrease in prothrombin in the blood. Vitamin K itself does not become a part of the prothrombin molecule, but it is essential for the production of prothrombin by the liver. A form of hemorrhagic disease in newborn infants is attributable to vitamin K deficiency. *In utero*, the fetus gets adequate amounts of vitamin K from the mother, but in the first few days after birth a deficiency may develop, presumably because bacteria which produce vitamin K have not yet become established in the digestive tract of the infant. To prevent a deficiency from occurring in the newborn, the mother is given vitamin K for several days before delivery, so that the stores in the fetus are increased, or the infant is given vitamin K soon after birth.

Water-Soluble Vitamins

Vitamin C. Scurvy, produced by lack of vitamin C, is considered to be the first disease definitely recognized to be associated with a dietary deficiency. Scurvy was known to occur regularly among sailors on long voyages when fresh foods were not available, and the curative value of fresh vegetables and citrus fruits was known at least as early as the fifteenth century. The following quotation from *Two Years before the Mast*, written by Richard Henry Dana in 1840, is an excellent description of scurvy.

The scurvy had begun to show itself on board. One man had it so badly as to be disabled and off duty; and the English lad, Ben, was in a dreadful state, and was gradually growing worse. His legs swelled and pained him so that he could not walk; his flesh lost its elasticity, so that if it were pressed in, it would not return to its shape; and his gums swelled until he could not open his mouth. His breath, too, became very offensive; he lost all strength and spirit; could eat nothing; grew worse every day; and, in fact, unless something was done for him, would be a dead man in a week at the rate at which he was sinking. The medicines were all gone, or nearly all gone; and if we had had a chest-full, they would have been of no use; for nothing but fresh provisions and terra firma has any effect upon the scurvy.

Vitamin C is ascorbic acid, a hexose derivative. It is easily oxidized, especially in the presence of copper; therefore, foods cooked in copper vessels lose their vitamin C content rapidly. It is speedily destroyed in alkaline solutions and is more stable in acid. There is a loss of vitamin C in dried foods, but not in frozen foods. The vitamin C requirement may

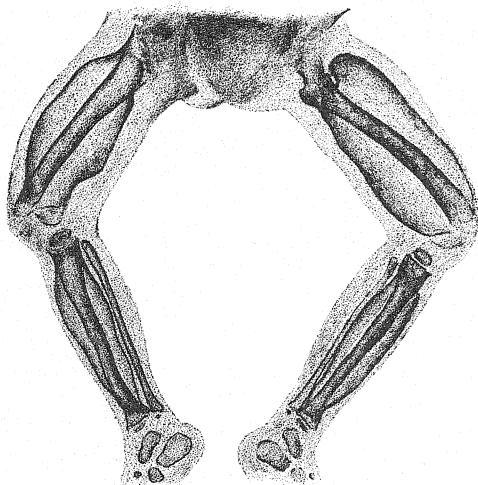


Figure 31-2. Effects of scurvy in a child.

This drawing is made from an X-ray film which shows the lifting of the periosteum away from the shaft of the bone as fluid accumulates under the periosteum. The posture is characteristic also; the child is supine with legs in a frog-like position.

be obtained readily from orange juice or tomato juice, and tablets of ascorbic acid are relatively inexpensive.

In scurvy, the gums become red and swollen and may show ulceration. There is bleeding from the gums and mucous membranes of the mouth and gastrointestinal tract. Calcification of the bones is defective and a characteristic change along the edge of the shafts of the long bones is seen on X-ray examination. In children with scurvy, the periosteum may

become widely separated from the shaft of the bone. This is especially obvious around the femur, and the thigh may appear swollen. The legs become quite tender to the touch and are held in a characteristic frog-like posture.

The recommended daily intake of vitamin C for adults is 30 to 75 mg. and for infants 10 to 30 mg. In growing children, a daily intake of 80 to 100 mg. is recommended. Higher amounts are desirable in pregnancy and during lactation.

Vitamin B complex. The vitamin B complex includes the following substances: thiamine (B_1), riboflavin (B_2 , G), niacin, pyridoxine (B_6), pantothenic acid, biotin, choline, inositol, para-amino benzoic acid, folic acid, and cyanocobalamin (B_{12}). Under some circumstances, the diet may be deficient in thiamine, riboflavin, or niacin, or all three of these substances.

Thiamine (B_1). Thiamine is a white crystalline compound having a yeasty odor. It is destroyed in acid solutions at the boiling point of water. Thiamine is found in whole grains, legumes, nuts, yeast, beef, and pork. Since it is water-soluble, like other members of the B complex, it is in some part discarded with the "cook-water." The daily requirement of thiamine under ordinary conditions is 1.5 to 2.5 mg. Under certain conditions, the requirement is considerably increased.

Thiamine, linked with phosphate, acts as a coenzyme which is essential for many metabolic reactions. Deficiency of thiamine in animals causes *polyneuritis*, a generalized involvement of peripheral nerves; and in man, a deficiency causes *beriberi*, which is characterized by polyneuritis, loss of appetite, muscular atrophy, chronic venous congestion, and edema. Death may occur from heart failure.

Riboflavin (B_2 , G). Riboflavin is an orange-yellow crystalline compound which is heat-stable in acid solutions, but is easily decomposed by light. It is found in milk, meats, eggs, and leafy vegetables. Riboflavin enters into combination with protein (flavoprotein) to form several "yellow enzymes."

Deficiency of riboflavin results in *cheilitis*, which is characterized by inflammation of the lips, fissures at the corners of the mouth, and scaliness, greasiness, and fissures of the folds of the nose and ears. The conjunctiva becomes dry, itchy, and inflamed. The daily requirement of riboflavin is 1-2 mg. for children and 2-3 mg. for adults.

Niacin. Niacin, or nicotinic acid, is a white crystalline compound which is stable in air and to heat. There is little loss in cooking, except

in the discarded "cook-water." It is found in meats, fish, eggs, whole grains, and peanuts. Niacin is a part of two important coenzymes, known as coenzymes I and II, which are members of enzyme systems concerned with cellular respiration and the breakdown of glucose.

A deficiency of niacin in dogs causes "*black tongue*." The animals refuse to eat, and the mucous membranes of the mouth, lips, and tongue become inflamed. Deficiency of niacin in man causes *pellagra*. This con-

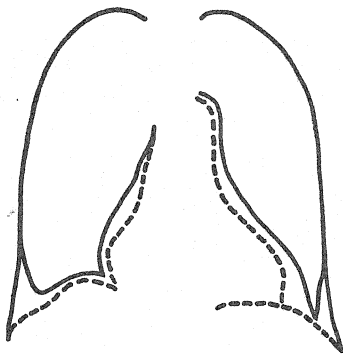


Figure 31-3. Cardiac silhouette of a patient with beriberi before and after three weeks of treatment with thiamine.

The outlines of the thoracic wall, heart, and diaphragm have been traced from the X-ray film. The heart and diaphragm outlines as seen before treatment are shown in solid lines and the outlines after treatment are shown by broken lines. For normal cardiac silhouette, see Figure 19-2, page 209.

dition formerly was prevalent in southern Europe and southeastern United States among low-income groups. It is characterized by soreness and inflammation of the mouth, pigmentation and thickening of the skin, and a symmetrical rash on the backs of the hands and arms. Diarrhea and nervous and mental disorders also are characteristic. Pellagrous individuals, however, usually are deficient in riboflavin and thiamine as well as niacin. The daily requirement of niacin is 4-20 mg. for children and 15-20 mg. for adults.

Pyridoxine. Pyridoxine is related chemically to niacin. Deficiency of pyridoxine causes dermatitis and swelling of the ears and paws in rats. This vitamin probably is required by man, but there is no knowledge of the symptoms resulting from a deficiency. For the most part, it is found in the same foods containing the B vitamins discussed above.

Pantothenic acid. Deficiency of pantothenic acid has been shown to produce symptoms in several species of animals. Probably it is required by man; however, it is so widely distributed and so little is required that development of a deficiency is unlikely.

Biotin. Biotin is widely distributed and, apparently, it is produced by intestinal bacteria. A deficiency is produced in experimental animals, not by limiting the amount of biotin in the diet, but by feeding a protein (avidin) found in egg white, which combines with biotin to form a compound that cannot be absorbed from the intestine. Deficiency of biotin in rats is characterized by scaliness of the skin, extensive dermatitis, swelling and redness of the lips, swelling of the paws, and involvement of the nervous system. The requirements in man are not known, and it is unlikely that a deficiency ever develops.

Choline. Choline is widely distributed, and deficiencies apparently do not occur in man. Deficiency in experimental animals produces fatty liver and other changes (page 355). There are close relationships between methionine and choline, each of which has labile methyl ($-\text{CH}_3$) groups.

Inositol. The role of inositol in human nutrition has not been determined, but, like choline, it is believed to be lipotropic.

Para-amino benzoic acid. Para-amino benzoic acid (PABA) is chemically related to the sulfonamide drugs. Large doses are non-toxic, but interfere with bacteriostatic effects of the sulfa drugs. PABA is widely distributed in foods. A deficiency in rats causes failure of lactation and graying of the hair. Effects of deficiency in man are not known.

Pteroylglutamic acid (folic acid). Pteroylglutamic acid and related substances are essential for the growth and maturation of red blood cells. These substances appear to be related to the dietary "extrinsic factor" which is required for normal production of red cell stroma. A deficiency of folic acid in the diet or failure to absorb it produces a macrocytic type of anemia. Folic acid is beneficial in the treatment of the macrocytic anemias secondary to sprue, pregnancy, pellagra, etc. Folic acid also has a favorable effect upon erythrocyte production in pernicious anemia, but it does not reverse the neurological changes seen in this disease. Requirements of pteroylglutamic acid in man are not known. The dosages per day in anemias are from 10 to 30 mg. intravenously or 200 mg. by mouth.

Cyanocobalamin (B_{12}). Vitamin B_{12} apparently is related to, or perhaps is, the substance which is lacking in patients having pernicious anemia (page 180). It is a complex substance with a minimum molecular weight

of around 1300. Each molecule of the compound contains an atom of cobalt. Vitamin B₁₂, administered by hypodermic in relatively small amounts, will reverse the changes in the blood seen in pernicious anemia and will arrest the neural changes. Vitamin B₁₂ is effective when given orally only if very large doses are used, since it is not absorbed readily by a patient with pernicious anemia. Normal gastric juice and extracts of the mucosa of the pylorus or of the duodenum greatly enhance the absorption of orally administered vitamin B₁₂. The actions of folic acid and vitamin B₁₂ are not yet completely understood, but it appears that they are concerned with the synthesis of nucleoproteins.

The disease, pernicious anemia, is not produced initially by a deficiency of vitamin B₁₂ in the diet; it develops because of failure of the individual to absorb the vitamin, and this in turn is related to the prior degeneration of the gastric mucosa which characterizes this disease. Why the gastric mucosa becomes atrophic is not known; and, although vitamin B₁₂, given by routes other than the oral, may relieve the patient of all of the symptoms of pernicious anemia, it will not bring about restoration of the gastric mucosa to its normal state.

Minerals

The inorganic elements which need to be included in the diet in considerable amounts are sodium, chlorine, calcium, potassium, phosphorus, magnesium, and sulfur. Iron and iodine are required in lesser amounts, and traces of copper, zinc, manganese, fluorine, and cobalt are needed. The functions of the inorganic substances are, in general, as follows: (1) they enter into the structure of bone and teeth (calcium, phosphorus, magnesium); (2) they are found in specific essential compounds such as hemoglobin (iron), thyroid hormone (iodine), methionine (sulfur), and vitamin B₁₂ (cobalt), or they are essential in certain enzyme systems (magnesium, manganese); (3) they provide a composition and osmotic tension of the fluid compartments favorable for metabolic processes and for the interchange of materials between these compartments (page 274). For the latter functions, Na⁺, K⁺, Ca⁺⁺, Mg⁺⁺, H⁺, OH⁻, and HCO₃⁻ are most important. Both the normal permeability of the cell membranes and the irritability of nerve and muscle fibers depend upon a fine balance between several of these ions. As regards irritability, the *ratio* is even more important than absolute amounts of the substances

(see page 220). The relationship may be expressed thus: irritability tends to be increased by an increase of Na^+ or K^+ above the usual range or by a decrease in Ca^{++} , Mg^{++} , or H^+ . Since K^+ and Ca^{++} are more subject to wide disproportionate variations in body fluids under abnormal conditions, they are the most important ions contributing to alterations in neuromuscular irritability.

Approximately 51 per cent of the total ash (inorganic residue) of the body is calcium and phosphorus, and potassium, sodium, chloride, and sulfur constitute about 14 per cent of the ash. Thus, six elements comprise about 65 per cent of the total mineral matter of the body. Some of the elements such as iron and iodine, which are present in small amounts, are very important and sometimes are not supplied in the diet in adequate amounts.

Sodium, potassium, and chloride. Sodium, potassium, and chloride make up by far the major part of the inorganic material in solution in the body fluids. Sodium and potassium do not pass readily through the cell membranes; sodium is the principal cation in the blood plasma and interstitial fluid, while potassium is the principal intracellular cation. The chloride ion is the anion present in the largest amounts in the extracellular fluid compartment, whereas PO_4^{---} is the principal anion in the intracellular fluid. The distribution of electrolytes in the blood plasma, interstitial fluid, and intracellular fluid is shown in Figure 31-4.

No special precautions to include NaCl in the diet of a normal person are necessary if the individual has free access to this substance. Furthermore, the normal person may eat any amount of salt that he desires. In a number of diseases, however, severe restriction of salt intake becomes necessary.

The distribution of Na^+ , K^+ , and Cl^- between intracellular and extracellular fluid is controlled, in part, by adrenal cortical hormone. When there is a deficiency of adrenal cortical activity, (1) there is increased urinary excretion of Na^+ and Cl^- and decreased concentration of these ions in the blood, (2) there is an increased level of K^+ in the blood, (3) there is a negative water balance associated with the negative salt balance, and the volume of the extracellular fluid decreases. Apparently, the disturbances are related in part to alterations in permeability of the cell membranes to K^+ and Na^+ and to influences of the adrenal cortical hormone on renal function (page 383). This hormone promotes reabsorption of sodium and inhibits reabsorption of potassium in the renal tubules. The abnormalities described above, among others, are observed in patients with Addison's disease in whom the adrenal cortex is damaged or destroyed.

Calcium and phosphorus. Calcium is concerned with (1) growth of bone, (2) coagulation of the blood, and (3) the maintenance of the normal permeability of membranes and irritability of muscle and nerve. Phosphorus is present in the body in both organic and inorganic compounds. Inorganic phosphorus is made available either by absorption or by liberation from organic combinations in the body by the action of *phosphatase* enzymes. It is used in the mineralization of bone and in the intermediary metabolism of organic foodstuffs.

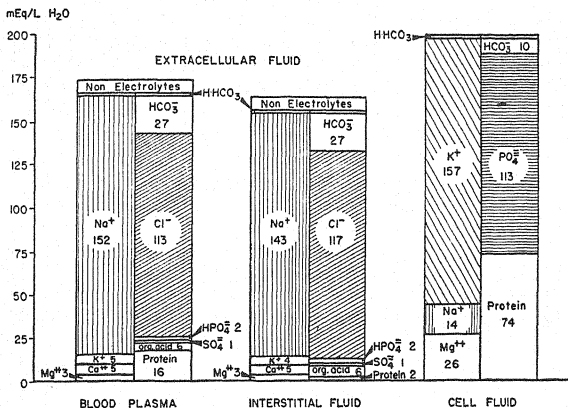


Figure 31-4. Comparison of composition of blood plasma, interstitial fluid, and cell fluid.

(Reproduced by permission from Newburgh, *Significance of Body Fluids in Clinical Medicine*. Copyright, 1950, by Charles C Thomas Publishers.)

Regulation of blood calcium level. (See also pages 399-401.) Blood serum normally contains 9 to 11.5 mg. per cent of calcium. It is present in two forms, *diffusible* and *non-diffusible*. The latter cannot pass through certain artificial membranes and is thought to be in chemical combination with protein; it is physiologically inert. The diffusible fraction, normally about half of the total (4.5 and 6 mg. per cent), contains the ionized physiologically active portion of the serum calcium. The calcium ion concentration in the blood is regulated within a narrow normal range largely

through the influences of parathyroid hormone and vitamin D. Injection of parathyroid hormone causes an increase in the blood calcium and in the urinary excretion of calcium and a decrease in the blood phosphorus. Parathyroid hormone maintains the blood level of calcium by causing mobilization of calcium from bone. Vitamin D promotes an increased absorption of calcium from the intestine and facilitates the deposition of calcium and phosphorus in bone.

Removal of the parathyroid glands is followed by a lowering of the calcium level of the blood and the development of *tetany*. In acute tetany, neuromuscular irritability is increased to such a level that spasm of the musculature of the hands and feet develops and a laryngospasm may be present also. Untreated experimental animals die in convulsions. Hypoparathyroid tetany may be relieved dramatically by intravenous injection of calcium gluconate or other calcium salts, or recurrence can be prevented for a time by treatment with parathormone.

Magnesium. Magnesium is found chiefly in bone and muscle. Its indispensability has been demonstrated in experimental animals, and presumably it is essential in man; however, it is questionable if a deficiency ever develops, and its functions cannot be definitely stated. Chlorophyll, the pigment in green vegetables, has a high magnesium content. The magnesium level in the blood is relatively constant, but little is known regarding the factors regulating it.

Iron. Iron is a component of hemoglobin and of chromatin material in the nucleus of the cell; it is concerned with the transport of oxygen and with oxidative processes in the tissues. In the absence of disturbances in absorption, and providing there is no loss of blood from the body, an equilibrium between intake and loss may be maintained in adults on 5 to 10 mg. per day. The iron from internal sources is about 20 mg. daily, resulting from the breakdown of hemoglobin, and this is several times the exogenous daily requirement. Inorganic iron salts are absorbed chiefly in the first part of the duodenum where the process is facilitated by the presence of the hydrochloric acid of the gastric juice. It appears that the normal organism absorbs iron from the intestine only as needed, any excess being lost in the feces; thus, the iron stores are controlled largely by regulation of absorption rather than by excretion. Erythrocytes are destroyed in the cells of the reticulo-endothelial system; the hemoglobin is broken down into globin and the pigment, *hematin*. Hematin is converted to hemosiderin, an iron-containing pigment, and then to a series of iron-free pigments terminating in bilirubin (page 336).

Copper and cobalt. On the basis of work on experimental animals, it is known that minute amounts of copper are needed for the formation of hemoglobin, especially for the rapid regeneration of hemoglobin after dietary anemias. In some experimental animals (cattle, sheep), anemia is produced by cobalt deficiency. Vitamin B₁₂ (page 368) contains 4.5 per cent of cobalt by weight. Small amounts of cobalt probably are essential in man, but it is unlikely that a deficiency would occur. The estimated daily requirement of copper for man is 2.0 to 2.5 mg. Copper is present in many foods, so that this amount usually is ingested.

Iodine. Iodine is present in the thyroxin molecule and in other compounds in the thyroid gland. More than one-half of the total iodine in the body is found in the thyroid gland (page 396). Blood contains only three to six micrograms per 100 ml. Although the iodine requirement is very small, there are large glaciated, inland areas of the United States and Europe in which the daily intake is deficient unless iodized salt is used. The iodine content of vegetables and, to some extent, of water depends upon the iodine content in the soil. Sea water contains iodine and hence deficiencies seldom occur in coastal regions. Deficiency of iodine results in the development of simple goiter (page 399).

Other trace elements. *Zinc* is present in the important enzyme, carbonic anhydrase (page 295), and possibly in other enzymes. *Fluorine* is present in varying amounts in teeth. Deficiency of fluorine in the drinking water causes an increased incidence of dental caries. *Manganese* has been shown to be an essential element in the diets of experimental animals, and some of the enzymes concerned with intermediary metabolism are more active in the presence of manganese. Probably it is necessary in man, but effects attributable to deficiency of manganese have not been described.

Chapter 32

EXCRETION

Most of the substances which must be eliminated from the body are in two major categories: (1) waste substances such as urea and CO_2 , which are being continually produced as a result of intermediary metabolism, and (2) substances such as sodium chloride and water which may be ingested in considerably larger amounts than are needed. The kidney and the lungs are the organs which are most concerned with maintaining a constant volume and composition of the fluid compartments of the body. The O_2 tension is kept up to normal and the CO_2 tension down to normal as a result of the interchange of these gases between the blood of the pulmonary capillaries and the alveolar air. The water and electrolyte content of the body is kept relatively constant as a result of the ability of the kidney to excrete any excess of these substances. Variable amounts of water, sodium chloride, and urea also are lost through the skin due to perspiration. The elimination of substances by this route, however, is incidental to other functions of the skin and sometimes is disadvantageous in that it continues even when there is a deficiency of salt and water in the body. A great number of foreign substances which have no function in the body also are eliminated by the kidney, while other foreign substances are excreted by the liver into the bile and thence into the intestine.

From the facts presented above, it is apparent that nothing very specific can be stated about the volume or composition of the urine. However, the average adult male on a mixed diet produces about 1200–1500 ml. of urine per day containing about 50–55 gm. of solids of which 25–30 gm. is urea and about 10 gm. is sodium chloride. The remaining 15 gm. of solids includes potassium, sulfate, phosphate, ammonia, calcium, magnesium, creatinine, uric acid, hippuric acid, and smaller amounts of many other substances. The specific gravity of the urine usually is in the range

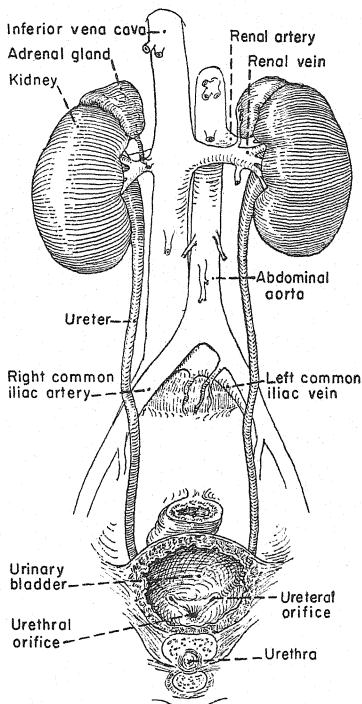


Figure 32-1. The parts of the urinary system.

between 1.010 and 1.025, but can be considerably lower or higher than this, depending upon the amount of water ingested. The kidney must excrete a considerable amount of solids per day and can do this independently of the amount of water ingested as long as the latter is above a certain minimum. When the amount of water exceeds the minimum

required, the specific gravity of the urine decreases correspondingly to approach that of water (1.000), and if huge amounts of water are drunk the urine will have a specific gravity only slightly above that of water.

Physiological Anatomy of the Kidney

The kidneys are bean-shaped organs located in the lumbar region on each side of the vertebral column (Figure 32-1). The physiological unit of the kidney is a structure known as a *nephron*, and it is estimated that

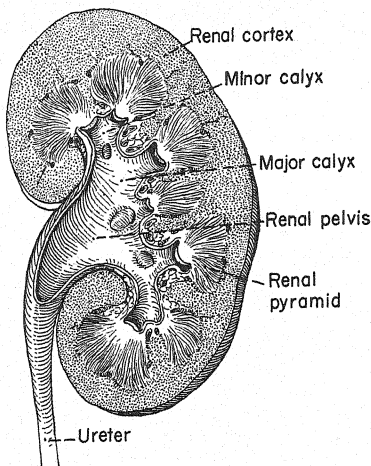


Figure 32-2. Longitudinal section of the kidney.

each kidney contains about one million of these units. Urine which is produced in the nephron passes from them into small conduits which empty into the pelvis of the kidney. From the pelvis, the urine flows into the *ureter* which is a muscular tube extending from the kidney to the *urinary bladder*. The two ureters empty into the bladder by separate

openings. The channel by means of which urine passes from the bladder during micturition is the *urethra*.

Since the nephron is the functional unit, it is necessary to know certain details concerning its structure. Each nephron is composed of a *vascular*

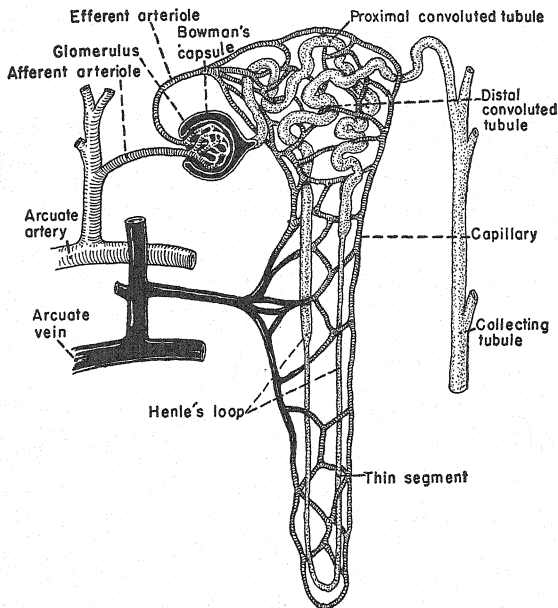


Figure 32-3. Diagram of the parts of a nephron.

portion and an *epithelial* portion. The most striking single portion of the nephron is the *glomerulus*, shown in Figure 32-3, and this may be considered as the initial portion of the nephron. In the glomerulus, a small artery is seen to break up into a tuft of vessels and to rejoin into a still smaller artery that leads out of the glomerulus. The first portion of the

epithelial element is the double-walled capsule surrounding the glomerulus. This structure is known as *Bowman's capsule*, and it is here that the formation of urine begins. By reference to the figure, it can be seen that Bowman's capsule is drained by a tortuous, minute tube, or *tubule*, and that the blood which flows from the glomerulus is carried to a capillary network supplying the tubule. Thus, the vascular element consists consecutively of (1) the *afferent arteriole* leading to the glomerulus, (2) the *glomerulus* itself, (3) the *efferent arteriole*, and (4) the *capillary bed* around the tubules. The epithelial element consists of (1) *Bowman's capsule*, (2) a *proximal convoluted tubule*, (3) the *loop of Henle* which is the U-shaped portion of the tubule extending down toward the pelvis of the kidney, and (4) the *distal convoluted tubule* which empties into collecting tubules. The loop of Henle itself consists of three portions: (a) a descending limb which is similar histologically and functionally to the proximal convoluted tubule, (b) the thin segment which consists of flat epithelial cells, and (c) an ascending limb composed of cuboidal epithelial cells which are similar in structure and function to those found in the contiguous distal convoluted tubule.

Mechanism of Renal Function

The initial step in the production of urine is the filtration of water and dissolved substances from the blood plasma across the glomerular wall into Bowman's capsule. The force promoting filtration is the pressure of the blood in the glomerulus. The pores in the membrane are of a size such that all of the smaller dissolved particles in the blood plasma are free to pass through, while the blood cells and molecules of plasma protein, for the most part, are retained in the blood vessel. As the filtrate flows down the renal tubule, large amounts of certain substances are absorbed from the tubule into the capillaries and some substances are passed from the blood into the lumen of the tubule. Thus, renal function involves three different processes: (1) glomerular filtration, (2) tubular reabsorption, and (3) tubular secretion. When the manner in which the kidney removes any given substance from the blood is the question under consideration, there are also three possibilities; all such substances are filtered through the glomerulus into Bowman's capsule, and as each substance passes down the tubule either it is not affected or it is in part reabsorbed or more of the substance is transferred into the tubule from the blood. In other

words, the amount of certain substances excreted is equal to the amount filtered, while in the case of other substances the amount excreted is either greater or less than the amount filtered because either tubular excretion or tubular reabsorption of these substances also occurs.

Glomerular filtration. The principal evidence that the glomerulus functions simply as a filter is as follows. First, the glomerulus discriminates between the different molecules in the plasma on the basis of size only. All of the smaller molecules pass through, and proteins such as egg albumen and gelatin, having a molecular weight of around 35,000, pass through, while larger protein molecules such as serum albumen (67,500 mol. wt.) and serum globulin (103,800 mol. wt.) normally do not pass through in significant amounts. In certain diseases in which the permeability of the glomerulus is increased, albumen appears in the urine in considerable amounts, while globulin is retained.

A second line of evidence that the glomerulus functions as a filter is that the concentrations of solutes in the capsular fluid are identical to the plasma concentrations of these substances. In experimental animals, minute amounts of capsular fluid have been removed through micropipettes and have been analyzed for urea, glucose, sodium, chloride, and other substances. All of these substances are present in the *capsular* fluid in concentrations similar to the concentrations in the blood plasma, but as the filtrate moves along the tubule the concentrations of these substances change greatly. For example, the concentration of glucose decreases, while the concentration of urea increases. The latter change occurs even though some of the filtered urea is reabsorbed in the tubule because water is reabsorbed even faster than the urea.

Finally, the balance of forces across the glomerular membrane, which are basically similar to those regulating interchange across the capillary wall (page 269), are adequate to cause filtration and any changes in magnitude of these forces produce the effects on filtration that would be predicted if only these physical factors are involved. The pressure of the blood in the glomerulus is around 65 mm. of mercury. Acting against this pressure is the osmotic pressure of the plasma, due to plasma protein, which is about 25 mm. of mercury, and a capsular hydrostatic pressure of about 10 mm. of mercury. Thus, there remains an effective filtration pressure of about 30 mm. mercury ($65 - 35$). If a ureter is obstructed, the capsular pressure rises to counterbalance the filtration when the pressure in the ureteral lumen reaches around 40 to 50 mm. of mercury, and no further production of urine occurs while the obstruction remains.

Alterations of glomerular filtration rate. The rate of glomerular filtration, abbreviated GFR, is altered if there are changes in either the plasma protein level, the pressure in Bowman's capsule, or the pressure in the glomerulus. However, under physiological conditions, only the latter undergoes considerable alterations. Changes in pressure in the glomerulus are produced subsequent to relaxation or constriction of either the afferent or efferent arterioles. The smooth muscle in these vessels is innervated by adrenergic vasoconstrictor fibers supplied by the sympathetic nervous system. Activation of these nerves, as by direct stimulation, usually causes a considerable decrease in the renal blood flow and a lesser decrease in the GFR. The decrease in blood flow occurs because resistance to flow has increased as a result of reduction in caliber of the arterioles, but the efferent arterioles may be constricted more severely than the afferent, and this serves to counteract the fall in pressure in the glomerulus. This can be visualized more readily if one analyzes what would happen if only the efferent arterioles should constrict; the resistance to flow of blood would increase and hence flow would decrease, but the pressure in the glomerulus "upstream" from the constriction would be increased and hence GFR would be increased.

Tubular reabsorption. That reabsorption by the renal tubules occurs is evident from the fact that some of the plasma constituents, which are freely filtrable and hence appear in the capsular fluid in concentrations similar to those in plasma, either do not appear in the urine at all or appear in amounts much less than the total amounts filtered. Substances which normally are entirely reabsorbed in the renal tubules such as glucose are known as *threshold* substances; as long as these substances are filtered in amounts below certain levels, they are completely reabsorbed, but, if the load presented to the tubule by glomerular filtration exceeds these levels, the substance appears in the bladder urine. Other substances, called *no-threshold* substances, are allowed to escape regardless of their level in the blood.

A large part of the filtered water, glucose, sodium, chloride, and urea passes back through the tubular epithelium into the blood. In fact, about 99 per cent of the filtered water and NaCl is reabsorbed. The passage of substances from the tubules back into the blood is accomplished in large part by the physical processes, diffusion and osmosis, since the hydrostatic pressure in the capillaries of the tubules is considerably lower than the pressure in the glomerulus and the osmotic pressure, due to plasma proteins, is greater in the blood reaching the capillaries supplying

the tubules than in the blood before filtration. The return of substances to the blood as a result of these passive processes is referred to, loosely, as "back-diffusion." However, in addition to back-diffusion, specific portions of the tubule possess the ability to reabsorb certain substances "actively." The epithelial cells of the renal tubules contain mechanisms which are concerned with transport of substances from the tubule into the blood, even though the concentration in the tubule may be considerably less than that of the blood. Complex enzymatic processes are involved. In general, the tubules can transport a certain maximal amount of a given substance such as glucose by active processes; when the amount presented to the tubule is less than this, the substance is reabsorbed completely and when the load is greater, the excess escapes into the urine. The tubular transport mechanisms also exhibit several other features which are characteristic of processes involving enzymatic action.

Tubular secretion. The epithelium of the renal tubules also has the ability to transfer certain substances from the blood plasma into the lumen of the tubule. Usually, tubular secretion is demonstrated and studied by the injection of substances not normally present in the body. Creatinine is a physiological substance which is not secreted by the tubules when the blood level is normal, but which is eliminated by tubular excretion in addition to glomerular filtration when a higher than normal blood level is produced by injection. The ammonia which is secreted by the tubules is not transferred from the blood, but is produced by the tubular epithelium (page 383). There is a maximum rate of tubular excretion of foreign substances such as *diodrast* and *para-amino hippurate*. The *tubular maximum* for such compounds is demonstrated by observing an increase in the amount excreted with increasing plasma concentrations up to a certain plasma level beyond which further increases do not result in further increases in the amount excreted.

Control of Renal Excretion of Water and Sodium Chloride

The rate of excretion of water by the kidney is controlled by the action of *antidiuretic hormone* (ADH) which is produced by the posterior portion of the pituitary gland (page 394). Approximately 125 ml. of water is filtered in the kidney per minute. This is about 180 liters per day, and, since normally less than two liters of urine is produced per day, the amount of water reabsorbed by the renal tubules is around 99 per cent

of the total filtered. In the complete absence of production of ADH, the amount of urine produced per day may be as high as 16 to 20 liters. Thus, it may be deduced that the kidney is capable of reabsorbing about 90 per cent of the glomerular filtrate without any influence of ADH, but to conserve water to the extent of reabsorbing an additional nine per cent, which brings the urine volume down to normal levels, the action of ADH is required. The disease which results when the posterior pituitary fails to produce ADH is known as *diabetes insipidus*. The word diabetes refers to an increase in the volume of urine produced. "Mellitus" means sweet, and "insipidus" means tasteless. The two types of diabetes differ as regards urine composition in that in *diabetes mellitus* the urine contains glucose, while in *diabetes insipidus* it does not contain sugar. Also, in the latter condition, the specific gravity of the urine is characteristically low. The patient having *diabetes insipidus* compensates for the water loss by correspondingly increasing his water intake.

When a normal subject drinks a large volume of water, the production of ADH by the pituitary is inhibited by mechanisms explained on page 394; consequently, reabsorption of water by the kidney decreases and the excess water is lost in the urine within a few hours. If one drinks 1500 ml. of water in the morning before eating, in which case the water will be rapidly absorbed into the blood, a similar amount of urine will be produced within the next four hours and the most dilute urine produced during this period may have a specific gravity as low as that which occurs in severe *diabetes insipidus*. This result signifies that liberation of ADH into the blood from the posterior lobe of the pituitary gland has been completely suppressed for a time following the ingestion of the 1500 ml. of water.

Osmotic diuresis. An osmotic effect is exerted by ions or molecules in solution in the fluid in the tubular lumen. Therefore, when substances such as sucrose or glucose are excreted, a certain minimum amount of water will be retained in the lumen because of the osmotic effect of the particles and the amount of water excreted will be increased. This is the mechanism of the increased urine production in *diabetes mellitus*. The more rapid the excretion of a substance by the kidney, the greater the amount of diuresis induced by the osmotic effects of the excreted particles. The diuresis produced by depression of reabsorption of certain substances by the tubule, as from phlorhizin, is another species of osmotically induced diuresis; glucose is excreted instead of being reabsorbed and water is carried out with it.

Anuria. Theoretically, lack of production of urine, or *anuria*, can be produced either by a failure of glomerular filtration or by complete tubular reabsorption of the filtrate. Failure of glomerular filtration is the basis for the anuria associated with a severe decrease in the arterial blood pressure, since there is insufficient hydrostatic pressure in the glomerulus. Urinary tract obstruction causes failure of glomerular filtration as the capsular pressure increases sufficiently to counteract the effect of the glomerular pressure.

Control of sodium and chloride reabsorption. The rate of sodium reabsorption varies with changes in the amount presented to the tubules. The reabsorptive mechanism is under the control of the adrenal cortex and of ADH. In the absence of production of adrenal cortical hormone, there is a decrease in sodium, and secondarily, of chloride and water reabsorption by the tubule; in the presence of an increased production of adrenal cortical hormone, the renal tubules are stimulated to take up sodium, so that less is excreted even though the amount of sodium filtered is maintained. When sodium is retained, reabsorption of chloride and of water secondarily is increased. ADH causes an increased excretion of sodium and chloride. These mechanisms are important in the homeostasis of the volume and composition of the fluid compartments.

Renal Regulation of Acid-Base Balance

The kidney has a major role in the maintenance of the *pH* of the blood within the normal range. In intermediary metabolism, a number of acid metabolites are produced. The residue from foods may be either alkaline or acid, and hence depending upon the diet, the body may be faced with the problem of elimination of an excess of either base or acid. Chemical changes occur in the kidney so that needed ions are conserved. When *conservation of base is required* or, in other words, when the problem is to eliminate acids, the *pH* of the urine may decrease to around 4.5, the excretion of bicarbonate ion decreases or ceases, chloride excretion increases, the kidney produces ammonium ion (NH_4^+) to be excreted with the anions, and more monobasic phosphate (NaH_2PO_4) is excreted instead of dibasic phosphate (Na_2HPO_4). In *alkalosis*, on the other hand, the *pH* of the urine increases to as high as 7.8, the excretion of bicarbonate increases, ammonium ion formation ceases, and the ratio of dibasic to monobasic phosphates in the urine increases.

Renal Clearance

Present knowledge of how individual substances are excreted by the kidney (that is, whether by filtration alone or by filtration and, in addition, either tubular reabsorption or tubular secretion) is based largely on studies of rates of "clearance" of substances from the blood plasma. Renal clearance, or *plasma clearance*, indicates the *volume of plasma that would contain the amount of substance excreted per unit of time*; or, if one is dealing with a substance which is completely removed from the blood flowing through the nephron, it is the amount of plasma which would need to flow through in order to permit excretion of the amount of the substance found in the urine. The formula for plasma clearance is as follows:

$$\text{Plasma clearance (min.)} = \frac{\text{Amount excreted (min.)}}{\text{Plasma concentration}} = \frac{U \times V}{P}$$

where U is the concentration of the substance in the urine, V is the volume of urine excreted per minute, and P is the plasma concentration. Thus, the determination of clearance involves knowledge of the plasma concentration of the substance during a given time period during which the total amount of urine produced is collected and the amount of the substance in the urine is determined.

Micturition

The wall of the urinary bladder contains layers of smooth muscle. This is known as the *detrusor* muscle. The triangular area between the orifices of the two ureters and the urethra is called the *trigone*. The smooth muscle in the first portion of the urethra serves as an *internal* sphincter and in males there is an *external* sphincter composed of striated muscle.

The act of *micturition*, or *urination*, is initiated by stretch of the bladder. It begins as a contraction of the detrusor muscle and shortly after this occurs the internal sphincter relaxes. Filling of the urethra reflexly promotes the continuation of the process.

The filling of the bladder occurs as urine is forced along the ureters and through the ureteral orifices by peristaltic waves. As the bladder fills, the tonus of the detrusor muscle adjusts so that only a slight rise in pressure accompanies a considerable increase in volume. This adjustment is accomplished in part by reflexes over the nerves which pass from the bladder to the spinal cord. As the bladder becomes filled to capacity, there is a greater rise in pressure with each increment of volume, and when a critical pressure level is reached, the "stretch" reflex which causes

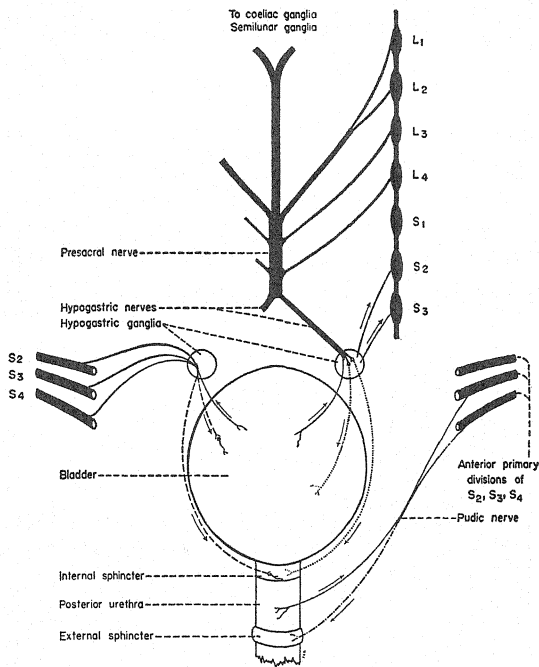


Figure 32-4. Diagram of innervation of the urinary bladder and urethra.

(Based on a description by Learmonth.)

emptying is elicited. The "stretch" reflex can be reinforced voluntarily to cause emptying when the bladder is only partly filled or it can be inhibited voluntarily until a somewhat greater pressure is reached.

The smooth muscle of the ureters is innervated by the sympathetic division of the autonomic system. The urinary bladder is innervated by the lumbar portion of the sympathetic system and by the sacral division

of the parasympathetic system. Stimulation of the parasympathetic fibers causes contraction of the bladder wall and inhibition of the trigone and internal sphincter of the urethra with the result that urination is produced. Stimulation of the sympathetic nerves to the bladder causes a fall in pressure at a given volume; also, the trigone contracts and the ureteral orifices are seen to be pulled toward the midline. Thus, sympathetic stimulation tends to inhibit micturition. As would be predicted from the effects just described, sympathomimetic compounds inhibit micturition and parasympathomimetic compounds promote micturition.

Chapter 33

THE HYPOPHYSIS

Organization of the Endocrine System

The principal endocrine glands are the thyroid, parathyroids, adrenal medulla, adrenal cortex, islets of Langerhans of the pancreas, testes in the male, ovaries in the female, and the anterior and posterior lobes of the hypophysis (also known as the pituitary gland) (Figure 33-1). Some of these glands apparently produce a single type of active material so that all of the influences of the gland can be mimicked by a single substance (thyroid, parathyroid, testis). The anterior lobe of the hypophysis, on the other hand, produces several hormones; the ovary produces two hormones, and it appears that several active substances are produced by the adrenal cortex.

The thymus and the pineal body sometimes are listed as endocrine glands, but they have not been definitely demonstrated to have endocrine functions. The intermediate portion of the hypophysis contains a substance, *intermedin*, which influences pigment-bearing cells of the skin in lower vertebrates. However, no function of this substance has been demonstrated in mammals.

Hormones are produced also in the mucosa of the stomach and duodenum. These substances influence motility of the stomach and gall bladder and cause secretion by the pancreatic, gastric, and intestinal glands. The mechanism of production and the actions of the gastrointestinal hormones are discussed in the section dealing with the physiology of the digestive tract. Epinephrine and acetylcholine (pages 106-110), which act as chemical mediators at neuroeffector junctions, sometimes are referred to as neurohormones. The neurohormones differ, however, from the other hormones in that they act at the site of their production and hence do not need to be transported by the blood.

For the most part, hormones regulate processes which are present in some degree in the absence of the hormones; and the endocrine glands themselves generally are regulated either by their nerve supply or by products of other endocrine glands. The anterior lobe of the hypophysis

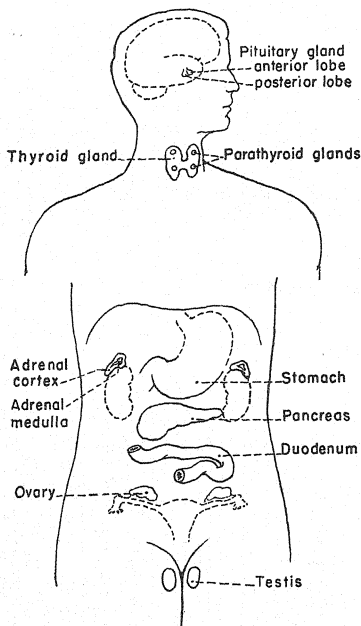


Figure 33-1. Locations of the endocrine glands.

is somewhat unique in that it produces several hormones each of which exerts its actions indirectly by influencing the production or liberation of a hormone by another endocrine gland, and some of the latter hormones may in turn depress the activity of the anterior lobe of the hypophysis. This gland produces hormones which directly influence the

thyroid, adrenal cortex, ovaries, and testes. The hormones of the anterior lobe apparently do not *directly* influence the parathyroid glands, adrenal medulla, or pancreatic islets. In addition, the anterior lobe produces substances which act directly on the tissues. The various types of mechanisms just described are illustrated in Figure 33-2. From this figure, it can be seen that the anterior lobe of the hypophysis serves as a sort of master gland of the endocrine system.

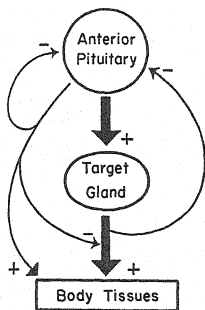


Figure 33-2. Diagram illustrating influences of the anterior lobe of the pituitary body.

The gland produces several active substances some of which act upon other endocrine glands, while others act directly on the tissues. The products of some of the "target" glands inhibit the production of the corresponding *tropic* substance by the pituitary.

the active substance produced by the gland than the venous blood flowing from the gland. This can be done readily in the case of the adrenal medulla. Not all of these criteria are met in the case of some of the endocrine glands, even though it is reasonably certain that the gland in question has endocrine functions. Failure to show greater amounts of hormone in the blood leaving the gland than in the blood reaching it may result simply from insufficiently sensitive methods for detection of the hormone. The hormones are noted for their ability to exert physio-

Proof that a Gland Has an Endocrine Function

Certain criteria may be set up which, ideally, should be met in order to establish unequivocally that a given gland has an endocrine function. First, removal of the gland should bring about changes in the organism. Abnormalities or deficits should appear. This is exemplified by the severe decrease in basal metabolism that occurs following removal of the thyroid gland. Second, an extract made from the gland should, on injection, be capable of counteracting or reversing the changes produced by removal of the gland. Third, if a sufficiently sensitive chemical or bio-assay method for detecting the hormone is available, one should be able to demonstrate that, at least under some conditions, arterial blood reaching the gland contains less of

logical actions in extremely high dilutions, and in some cases they can be detected by biological tests (bio-assay) when chemical tests are not sufficiently sensitive or specific.

It is apparent from the frequent reference to the actions of hormones in other sections of this book that the endocrine glands do not constitute a system which can be considered separately from other systems; however, it is desirable to describe the endocrine system as a unit, even though some repetition is necessary.

Anterior Lobe of the Hypophysis

The pituitary body, or *hypophysis cerebri*, is attached to the hypothalamus by a stalk known as the infundibulum (Figure 38-1, page 435). The pituitary is divided into an anterior lobe or adenohypophysis (*adenoglandular*) and a posterior lobe or neurohypophysis. The anterior and posterior lobes develop from different structures and have quite different functions. The anterior lobe contains three specific types of cells, *acidophil* (alpha), *basophil* (beta), and *chromophobe* cells. The latter, which are also known as chief or reserve cells, make up 50 per cent of the total and are considered to be precursors of the acidophil and basophil cells.

The vascular supply of the hypophysis is distinguished by the presence of a portal system in which the capillaries of the stalk collect into venules, then split up into sinusoids in the substance of the anterior lobe, and re-collect into veins which drain into the *cavernous sinus*. The supraopticohypophyseal tract which passes from the hypothalamus to the posterior lobe is described elsewhere (page 394).

The anterior lobe of the hypophysis produces several hormones. The principal effects of these substances are presented below.

1. *Somatotropin* (somatotropic hormone, growth hormone) stimulates the growth of the body. A deficiency occurring in the immature individual results in cessation of growth and hence in *dwarfism*. This type of dwarf has symmetrical proportions and is thus distinguished from the achondroplastic dwarf who has disproportionately short extremities. An excess of somatotropin in the young animal produces excessive proportionate growth resulting in *gigantism*. In the adult, an excess of growth hormone causes subperiosteal bone growth and enlargement of the viscera resulting in the disease known as *acromegaly*.

2. *Adrenocorticotropin* (adrenotropin, corticotropin, ACTH) is thought to originate in the basophil cells. It stimulates the adrenal cortex to produce and liberate one or more hormones, and has no direct effect on the

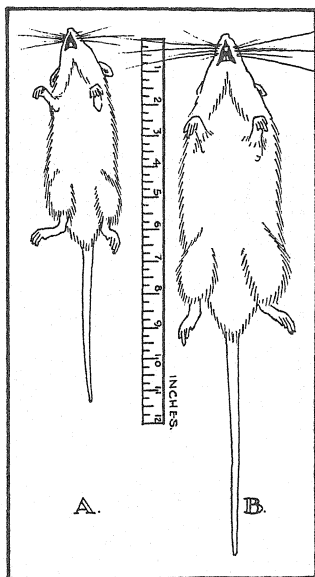


Figure 33-3. Effect of removing the pituitary gland from a young rat.

A, rat with pituitary removed. B, normal rat of the same age. (Reproduced by permission from Amberson and Smith, *Outline of Physiology*. Copyright, 1939, by Williams and Wilkins.)

adrenal medulla. A lack of ACTH is associated with atrophy of the adrenal cortex and an increase in sensitivity to stress. The specific effects of an increase in ACTH, usually produced by injection, are limited to those caused by an increased secretion of adrenal cortical hormones.

3. *Thyrotropin* stimulates growth of the thyroid and secretion of thyroid hormone. In the absence of thyrotropin, the thyroid becomes atrophic and the epithelium surrounding the follicles regresses to a flattened form. The characteristic picture of severe hypothyroidism develops. The basal metabolic rate may decline to 40 per cent below the average for normals.

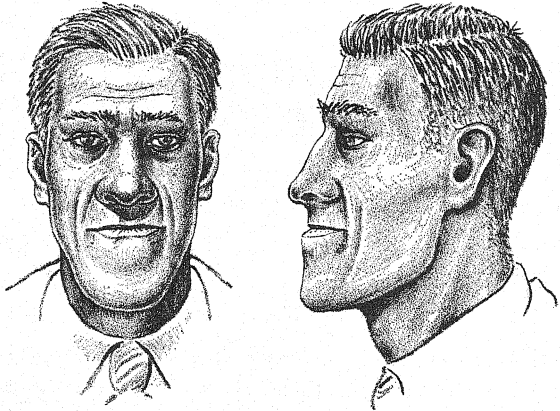


Figure 33-4. Appearance of person with acromegaly.

An excess of thyrotropin produces growth and multiplication of the follicular epithelium of the thyroid and the general features of hyperthyroidism are produced. In normal subjects, it is believed that thyroid hormone inhibits the production of thyrotropic hormone by the pituitary. Exophthalmic goiter, or Graves' disease, is considered to be a manifestation of hyperthyroidism secondary to stimulation of the thyroid by thyrotropin.

4. *Follicle-stimulating hormone* (FSH) is a substance produced by the anterior lobe of the pituitary in both males and females. In the male, it stimulates the proliferation of the seminiferous epithelium of the testes and has no effect on the interstitial cells. In the female, it stimulates growth and division of the granulosa cells of the immature follicle of the

ovary. A deficiency is associated with failure of growth of the ovarian follicles or regression of the seminiferous tubules of the testes.

5. *Luteinizing hormone* (LH, interstitial cell stimulating hormone, ICSH) is produced by the anterior pituitary in both sexes. In the female, it appears to stimulate the production of follicular hormone, or estrogen, by the granulosa cells and to stimulate growth of theca cells. It does not appear to produce secretion of hormone by the corpus luteum and will not prevent atrophy of the corpus luteum. In the male, it stimulates the development of Leydig cells and their secretion of androgen.

6. *Prolactin* (luteotropic hormone, LTH, lactogenic hormone) serves to maintain the corpus luteum and to promote the secretion of luteoid hormone. It stimulates lactogenesis in the fully developed mammary gland. Its action on the ovary is potentiated by the presence of follicular hormone. The three hormones of the anterior lobe of the hypophysis which are concerned with control of the endocrine functions of the ovaries and testes (FSH, LH, and LTH) are known collectively as *gonadotropic* hormones.

Crude pituitary extracts have actions which have not been clearly attributable to specific fractions. These actions probably are due to combinations of effects of the known hormones.

A *pancreatotropic* action has been postulated, due to the fact that the pancreas increases in size and in insulin content upon repeated injections of anterior pituitary extract. However, this effect may be explained on the basis of the elevation of blood sugar, due to adrenocorticotropin action; moreover, removal of the hypophysis fails to induce any involution of the pancreas. A specific *parathyrotropic* hormone is questioned because of the failure of hypophysectomy to induce atrophy of the parathyroids. The enlargement which occurs on injection of anterior pituitary extracts may be explained on the basis of metabolic alterations, notably the increased excretion of calcium secondary to the stimulation of the thyroid.

Two effects on carbohydrate metabolism occur which are not entirely accounted for by somatotropin and adrenocorticotropin. (1) The *glycotropic* action is the phenomenon of insulin resistance which occurs upon administration of anterior pituitary extracts. (2) The *glycostatic* action derives its name from the ability of anterior pituitary extracts to arrest the rapid loss of muscle glycogen in the hypophysectomized animal. Anterior pituitary extract tends to restore the muscle glycogen, and the effect is considered to be greater than can be accounted for on the basis of the actions of adrenocorticotropin alone.

Posterior Lobe of the Hypophysis

Two striking actions are exerted by small doses of unfractionated extracts of the posterior lobe: the *antidiuretic* action and the *oxytocic* action.

(1) **Antidiuretic hormone** (ADH, vasopressin, Pitressin). The renal effects of ADH are described on page 382. An increase in water intake inhibits antidiuretic hormone secretion, while a restriction of water stimulates its secretion. The liberation of antidiuretic hormone in response to

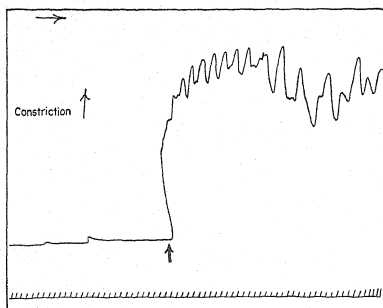


Figure 33-5. Oxytocic effect of pituitrin.

The record shows motility of the uterus of a pregnant guinea pig. At the arrow, a small quantity of pituitary extract was added to the liquid in contact with the uterus. (Courtesy of H. H. Dale.)

an adequate stimulus has been shown to depend upon an intact supra-opticohypophyseal tract, and also in some way upon the presence of the anterior lobe of the pituitary. For further discussion of control of secretion and mechanism of action, see pages 381-383.

The constrictor effect of vasopressin is directly on the smooth muscle of the walls of the blood vessels. The dose required to produce vasoconstriction is many times as great as that required to produce antidiuresis. There is no acceptable evidence at present that this compound has a physiological role in the control of the arteriolar tonus in man, and such

an action seems unlikely in view of the amount required to produce vasoconstriction.

(2) **Oxytocic principle** (pitocin). This substance, like ADH, is a polypeptide which is present in posterior pituitary extracts. One of its most striking actions is the induction of contraction in the pregnant uterus. The uterus is relatively unresponsive in the earliest stage of pregnancy, but as the pregnancy progresses, the gravid uterus becomes more and more responsive. The material is assayed commercially by measurement of its capacity to induce contraction of a suspended horn of gravid guinea pig uterus. Small doses augment the tonus of the uterine musculature and increase the strength of contraction, and larger doses produce a tetanic contraction. Although parturition is possible in some mammals after hypophysectomy, there is considerable evidence that the pituitary has a physiological role in the control of uterine motility.

When a severe deficiency of thyroid activity develops in an adult, the condition known as *myxedema*, or Gull's disease, results. This disease also is characterized by a severe reduction in BMR. The striking clinical manifestations are mental dullness, infiltration of the subcutaneous tissues with a mucoid substance, loss of hair, and a characteristic dull, bloated appearance of the face. The pulse is slow and of reduced strength and the blood pressure is low. All of these abnormalities can be reverted by treatment with suitable amounts of thyroid hormone.



Figure 34-2. Appearance of person with myxedema.

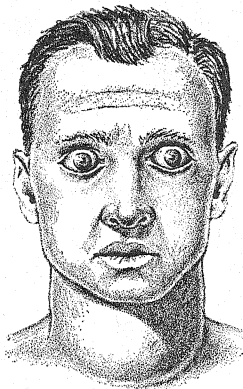


Figure 34-3. Appearance of person with exophthalmic goiter.

Excessive thyroid activity. An increase in thyroid activity above the normal level occurs as a result of tumors of the gland or because of overstimulation of the thyroid by thyrotropic hormone from the anterior pituitary gland. The condition produced in the latter case is known as *exophthalmic goiter*, or Graves' disease; exophthalmia refers to the characteristic protrusion of the eyeballs so that the patient appears to be staring. The BMR is elevated, pulse is rapid and full, the skin is warm, and the patient shows intolerance to heat. Persons with Graves' disease also are quite excitable and have a fine tremor. Hyperthyroidism can be relieved by removing the tumorous portion of the gland or, in the case of

Graves' disease, by removing the major part of the gland. Recently, drugs have been developed which are quite effective in depressing thyroid function.

Regulation of secretion of thyroid hormone. The control of secretion of thyroid hormone appears to be entirely humoral. The anterior lobe of the pituitary produces a hormone, *thyrotropin*, which stimulates the thyroid gland. Following injections of extracts containing thyrotropin, the secretory cells of the thyroid increase in size and number, and the amount of colloid in the follicles decreases. Basal metabolism is proportionately increased, and the picture which is typical of hyperthyroidism develops. It is believed that under normal conditions the hormone produced by the thyroid gland exerts an inhibiting influence on the output of thyrotropin by the pituitary. Just how this balance becomes disrupted in Graves' disease is not known.

Effects of iodine deficiency. When the daily intake of iodine is below that needed by the thyroid gland, an overgrowth of the gland occurs and the follicles become distended with colloid. Up to a certain point, the changes in the gland are reversible if iodine is supplied in sufficient amounts, but, when the deficiency of iodine is severe and prolonged, the gland may remain enlarged even when iodine is supplied. In most persons with simple goiter, the enlarged thyroid gland liberates a normal amount of hormone, hence neither hypothyroidism nor hyperthyroidism occurs in the typical case. It is now recognized that the soil in many inland, glaciated areas is deficient in iodine, and the use of iodized salt by populations in these regions has resulted in virtual disappearance of simple goiter.

The Parathyroid Glands

There are two pairs of parathyroid glands. They lie adjacent to, or are embedded in, the posterior aspect of the thyroid gland. Each gland is about the size of a pea. The cells of the parathyroid glands, unlike the thyroid, are densely packed. In some cases, especially in carnivores, there are accessory parathyroid glands located at other sites in the cervical region.

The major role of the parathyroid glands is the regulation of calcium and phosphorus metabolism (see page 371). The effective stimulus to parathyroid activity is considered to be a low level of calcium in the blood

plasma. This may be brought about by a diet low in calcium or high in phosphate or acid.

Effects of parathyroid insufficiency. A moderate lack of parathyroid hormone gives rise to a condition known as "latent" tetany. In this situation, the subject is apparently normal and without symptoms unless placed under stress. Pulmonary hyperventilation (due to heat, exercise, or emotional tension), a meat diet (high phosphate), and pregnancy are stresses which may evoke symptoms. The symptoms are the result of increased irritability of the nervous system, and increased neuromuscular excitabil-

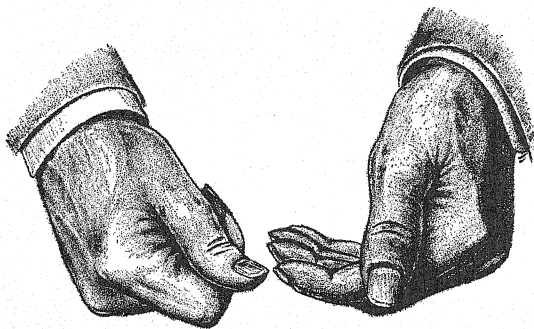


Figure 34-4. Appearance of hands of a person in tetany.

Spasm of muscles of the hands and wrists causes this characteristic position.

ity related to the lowered level of ionizable calcium in the blood. The hyperexcitability manifests itself mainly in the form of tremor and muscular twitches.

In the presence of acute lack of parathyroid hormone, frank tetany develops. This is best seen in the experimental animal from which the glands have been removed surgically. In the immediate postoperative period, there is a marked loss of appetite accompanied by great thirst, and the animal is depressed. After a period of about one to four days, the depressed state gives way to increasing excitability and restlessness, with spontaneous muscular twittings. Muscular tone increases, and the gait is altered. The temperature rises, and heart rate and respiratory rate increase. The pulmonary hyperventilation precipitates the final episode,

since the blowing off of carbon dioxide and the consequent increase in the pH of the blood causes a further increase in neuromuscular irritability. The twitchings shortly give way to generalized convulsions, and the animal dies in asphyxia from spasm of the glottis and the respiratory muscles unless the train of events is reversed by the injection of calcium salts. All of the symptoms are dramatically relieved by injection of calcium gluconate. Parathyroid tetany also may be averted by injection of parathyroid hormone, or by a high calcium, low phosphorus diet, and administration of large doses of vitamin D.

Effects of excess of parathyroid hormone. Administration of parathyroid extract reverses the sequence of events which follows removal of the glands. Blood phosphate decreases, calcium increases, and neuromuscular irritability returns toward normal. Effects of an excess of this hormone may be observed either following injection of repeated doses or in certain disease states. However, when injection is long continued, the animal becomes refractory to the substance. The administration of parathyroid hormone results first in increased renal excretion of phosphate, then a fall in blood phosphate and a rise in blood calcium, followed by an increased urinary calcium excretion. The long term effects of hyperparathyroidism are those which result from the altered mineral metabolism. Demineralization of bone is one of the commonest accompaniments of hyperparathyroidism.

Chapter 35

THE ADRENAL GLANDS AND PANCREATIC ISLETS

An adrenal gland is located on the superior pole of each kidney. Each adrenal, or suprarenal, gland consists of two histologically distinct portions, the cortex and the medulla. So far as is known at present, these two parts function as though they were completely separate glands. In fact, in lower vertebrates the tissue which corresponds to the adrenal cortex of mammals is found in separate bodies known as interrenal glands.

The Adrenal Medulla

The function of the adrenal medulla is to produce the hormone *epinephrine* and a closely related substance, *nor-epinephrine*. The two substances may be referred to collectively as catecholamines or *adrenomimetic* compounds. It will be recalled that many of the postganglionic neurons of the sympathetic nervous system exert their actions by liberation of epinephrine or nor-epinephrine. In addition, there are bodies of "chromaffin" tissue located in or near the sympathetic ganglionated chains and preaortic ganglia, and presumably this tissue also can liberate epinephrine. The amount of the extra-adrenal chromaffin tissue varies considerably from one species to another.

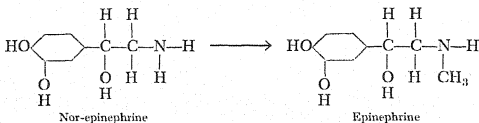
Physiologically, adrenomimetic compounds are liberated from the adrenal medulla only as a result of impulses reaching the cells by their nerve supply. The cells of the medulla correspond to adrenergic neurons of the sympathetic system; they are innervated by preganglionic neurons of the thoracolumbar system. The medullary portion of the adrenal

glands may be destroyed by cautery, and, when this is done, the animals not only survive, but they show no striking changes. This is true mainly because the adrenomimetic compounds have actions which supplement those of the adrenergic part of the autonomic system; thus, when the adrenal medullae are destroyed, a mechanism remains which can compensate for the loss. The sympathetic system has been removed completely in cats and dogs. In the totally sympathectomized animals, there is no physiological mechanism for liberation of catecholamines from the adrenal glands, since the innervation of the medulla is destroyed, and there are no functional thoracolumbar pathways. The animals survive and, in fact, show no striking abnormalities under ordinary laboratory conditions; however, their ability to cope with emergencies is impaired. For example, in such animals, there is a much greater decrease in blood sugar level in response to a given dose of insulin than occurs in the normal, or, when the room temperature is lowered, they will shiver at higher temperatures than those required to produce shivering in normal animals.

Emergency function. The sympathoadrenal system is relatively inactive under resting conditions and is brought into activity in emergencies. Many of the conditions under which catecholamines are liberated by the adrenal medulla have been discussed in other connections. These include hemorrhage, asphyxia, hypoglycemia, fright, rage, etc. In the situations in which catecholamines are liberated, they cause changes which, in one way or another, improve the chances of the organism for survival. Most of the irritable tissues in the body are affected by epinephrine. Smooth muscle in some organs is contracted (pilomotor muscles, radial muscle of the pupil, nictitating membrane, capsule of the spleen, sphincters of the gastrointestinal and urinary tract, various arterioles, etc.); smooth muscle in other organs is inhibited (gastrointestinal tract exclusive of sphincters, bronchioles, fundus of the urinary bladder, and possibly coronary arterioles). The rate and strength of the heart beat are increased, and there is an antifatigue effect on skeletal muscular contraction. Glycogenolysis is accelerated so that the blood glucose level is increased. The anterior lobe of the pituitary gland is stimulated by epinephrine to increase its output of adrenocorticotrophic hormone and this sets in motion the slower-acting humoral mechanisms that are of value in counteracting stresses of longer duration.

Production of epinephrine and nor-epinephrine. Tyrosine and phenylalanine most likely are the precursors of the adrenergic neurohormones

and of the active substances produced by the adrenal medulla. The intermediate stages are not definitely established. It is probable, however, that addition of the methyl group to nor-epinephrine is the final step in the production of epinephrine, and under certain conditions nor-epinephrine itself is liberated. It has been suggested that some cells in the adrenal medulla produce epinephrine, while others produce nor-epinephrine.



The Adrenal Cortex

The adrenal cortex is essential to life. Extirpation of the gland quickly results in vomiting, diarrhea, dehydration, decreased production of urine, and a steady decline in blood pressure leading to a shock-like state and death. The adrenal cortex has profound influences on carbohydrate, protein, and mineral metabolism, and on sex differentiation and function.

Types of cortical hormones. The exact nature and number of adrenal cortical hormones is not yet clear. Crude extracts of adrenal cortex yield a large number of compounds, and the active substances are separable into three broad groups on the basis of physiological effects: (1) the *sugar-active* compounds primarily affecting carbohydrate metabolism; (2) the *salt-active* compounds primarily affecting sodium, potassium, and chloride distribution and balance; and (3) *androgenic* and *estrogenic* substances which influence the development of secondary sexual characteristics. All of these compounds are steroids.

Cholesterol and ascorbic acid are found in considerable amounts in the adrenal cortex, and evidently these compounds are used in the production of cortical hormone, since they are depleted rapidly when the gland secretes. The adrenal cortex maintains a basal level of secretion independently of the action of ACTH. This is indicated by the fact that less cortical extract is required in the individual with hypopituitarism than in patients with Addison's disease in whom the adrenal cortex is completely destroyed. The current concept is that ACTH regulates the rate of release of the hormone above the basal level.

Apparently, the liberation of ACTH can be elicited by epinephrine reaching the pituitary gland by the circulation or by neural influences from the hypothalamus. In the latter case, it is suggested that the active substance, possibly epinephrine produced by adrenergic nerves, is carried to the anterior pituitary by a small portal system in the hypophysis. Following an increased output of ACTH, this substance is carried to the adrenal cortex where it causes an almost immediate increase in the output of adrenal cortical hormone.

The condition which is produced in man by chronic deficiency of adrenal cortical hormones is known as *Addison's disease*. This is sometimes produced following tubercular involvement of the adrenal cortices, bilaterally. Addison's disease is characterized by loss of weight, low blood pressure, low body temperature, severe muscular weakness, and a very characteristic bronzing of the skin. The changes seen in Addison's disease may be counteracted by treatment with adrenal cortical extract.

Actions of cortical hormones.

(a). *The sugar-active fraction.* This fraction is represented by steroids known as Compound E and Compound F. These compounds can correct the hypoglycemia of a patient with Addison's disease; they elevate the blood sugar of a normal individual, and they make a diabetic patient more resistant to insulin. These effects are accomplished in part by increasing the rate of gluconeogenesis.

(b). *The salt-active compounds.* The actions of desoxycorticosterone are representative of the salt-active group of compounds. These compounds primarily affect the exchange of sodium, potassium, and chloride. They produce an increase in renal tubular reabsorption of sodium, elevation of plasma sodium, increase in the ability of the kidney to concentrate potassium, and a decrease in plasma potassium.

(c). *The androgenic and estrogenic substances.* The production of androgenic and estrogenic steroids by the adrenal cortex appears to be separate from that of other fractions. Apparently, the production of this type of compound is regulated by gonadotropic hormones rather than by adrenocorticotrophic hormones. In Addison's disease, the excretion of these compounds is diminished. The diminution in axillary and pubic hair is considered to be a reflection of the loss of the fraction; and conversely, an increase in production results in the *adrenogenital syndrome*. The commonest manifestation of an excess in the female is the development of male characteristics, and in the male, precocious puberty is produced.

Adrenalectomized animals can be kept alive and virtually in normal

condition by injection of adrenal cortical extract and provision of adequate sodium chloride in the diet. Such animals have been maintained for long periods, simply by providing them with as much salt water as they want to drink and injecting desoxycorticosterone.

The Pancreatic Islets

The islets of Langerhans in the pancreas contain several types of cells among which are the *beta* cells which produce insulin. The actions of insulin are described in the discussion of the homeostasis of the blood sugar level and the endocrine control of carbohydrate metabolism (pages 355-357).

The effective stimulus for liberation of insulin appears to be an elevation of the level of glucose in the blood. As the blood sugar level rises following digestion of carbohydrate or during an intravenous injection, the output of insulin increases and this promotes the conversion of glucose to glycogen in the liver.

A deficiency in the production of insulin results in the disease, diabetes mellitus (see page 356). Secretion of an excess amount of insulin may occur as a result of simple overactivity of the islet cells, but, occasionally, a tumor of the islet cells produces excess amounts of insulin. The characteristic change in such cases is a fall in the fasting blood sugar level to as low as 20 to 30 mg. per cent; other changes which occur in hyperinsulinism are secondary to the low blood sugar (page 358).

There is evidence that the *alpha* cells of the islets produce a polypeptide known as glucagon which, on injection, produces hyperglycemia. Whether glucagon is important physiologically in the regulation of the blood sugar level is not clear, since it is not known whether it is liberated into the circulation in effective amounts under physiologic conditions.

Chapter 36

ENDOCRINE FUNCTIONS OF THE SEX GLANDS

The Testes

The testes have two functions, the production of the male sex cell, or *sperm*, and the elaboration and release of the male hormone, testosterone. Each testis is divided into conical lobules containing the seminiferous tubules in which spermatogenesis occurs (page 418). Microscopically, one sees in the transected testis the more or less circular tubules containing spermatogenic cells in various stages of development, and in between the tubules there is a supporting framework of connective tissue and blood vessels which contains characteristic cells known as *interstitial*, or *Leydig*, cells. It is believed that the interstitial cells produce testosterone.

The production of testosterone is controlled by the gonadotropic hormones of the pituitary gland. The gonadotropic hormone in the male which stimulates the Leydig cells is known as *interstitial-cell stimulating hormone*, or ICSH; however, it is the same substance which in the female is called *luteinizing hormone*, or LH. The substance FSH, which is named for its follicle-stimulating effect in the female, also occurs in the male where it exerts an influence on the epithelium of the seminiferous tubules.

There is a balance between the action of gonadotropic hormones and the output of androgenic and estrogenic substances. This is indicated by the fact that production of the latter substances decreases if pituitary activity is impaired and, on the other hand, injection of estrogens or androgens causes a decrease in the output of gonadotropic hormones by the pituitary.

Effects of male sex hormone. The male sex hormone is essential for the normal development of the male secondary sexual characteristics such as growth of the beard, enlargement of the larynx and change of voice at puberty, development of masculine configuration of the body, and growth

of the male sex organs. If the testes are destroyed before puberty, *eunuchoidism* is produced. In this condition, the long bones overgrow because the epiphyses of the bones fail to close at the normal time. The musculature is poorly developed and fat tends to be distributed according to the pattern seen in females. The external genitalia do not develop, and

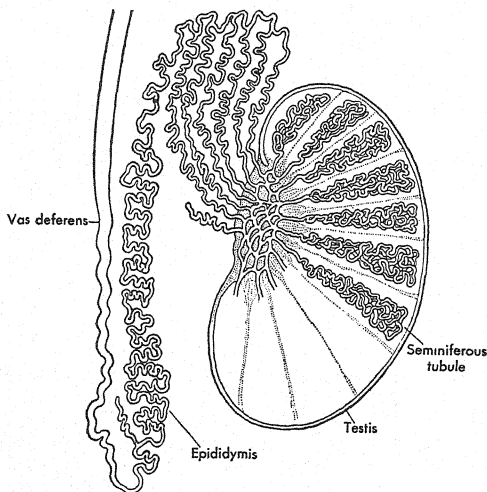


Figure 36-1. Diagrammatic section of the testis.

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the distribution of hair resembles that of the female. Loss of testicular function in the fully developed male is associated with retrogressive changes in the secondary sexual characteristics and decrease or loss of libido and potentia.

An excess of male sex hormone in male children produces precocious puberty. The greatest effects of testosterone are seen in individuals who are deficient, namely, in eunuchs and elderly persons. In normal adult

males, the effects are not striking, and, furthermore, the output of gonadotropic hormone by the pituitary is inhibited, so that the production of testosterone by the testes is correspondingly decreased and some degree of testicular atrophy is induced.

The Ovaries

The ovaries are paired organs which produce the female sex cell, or ovum, and elaborate two hormones which determine the female secondary sexual characteristics and cause cyclic changes in the lining of the uterus. The ovary is bean-shaped and is approximately $2\frac{1}{2}$ cm. wide and

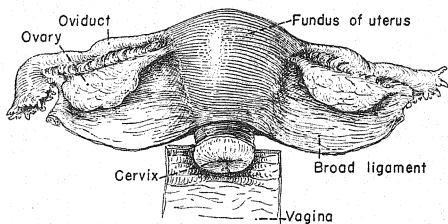


Figure 36-2. Female reproductive organs.

4 cm. long. The epithelial covering of the ovary or germinal epithelium apparently gives rise to the ova. In the adult, ova are found in large numbers and are concentrated in the cortical portions of the ovary. Each ovum is contained in a structure called a primary follicle (Figure 36-3). The ovum is surrounded by a layer of follicular cells which is separated from the interstitial connective tissue by a basement membrane. The development of a primary follicle consists of changes in the ovum, in the follicular cells, and in the adjacent connective tissue. The growing follicle enlarges mainly through an increase in the number of follicular cells so that the single layer is replaced by several layers, and, as this occurs, the ovum assumes an eccentric position. Next, irregular spaces containing liquid develop between the follicular cells, and the increase in amount of liquid causes a further enlargement to form the *Graafian follicle*. During the growth of the follicle, the surrounding connective tissue becomes

differentiated into a capsule or *theca*. The theca becomes subdivided into two layers, the *theca interna* which is adjacent to the basement membrane, and the *theca externa* or outer layer. These layers become more prominent as the follicle enlarges, but they are not sharply demarcated from each other or from the surrounding connective tissue stroma of the ovary.

The mature Graafian follicles are vesicles which bulge on the surface of the ovary. The follicular epithelium lining the cavity is called the *membrana granulosa*. The superficial part of the wall of the mature

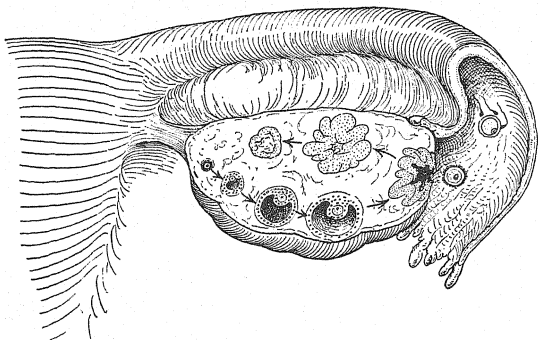


Figure 36-3. Section of ovary.

Different stages in the development of the follicle, release of the ovum, and formation of the corpus luteum are illustrated.

follicle becomes thinner and thinner and finally ruptures. The follicular fluid then oozes out into the peritoneal cavity and the ovum breaks loose from its connection with the follicular cells.

After rupture of the follicle and discharge of the fluid and ovum, the wall of the follicle collapses and the *membrana granulosa* is thrown into folds. The follicular cells and those of the *theca interna* change into large pale-staining cells. At this stage, the structure is known as the *corpus luteum* (*corpus*—body, *luteum*—yellow). The cavity is stellate in shape, due to the folds of the *membrana granulosa*, but the *theca externa* remains

ovoid. The cells of the theca interna accumulate in triangular masses at the base of the folds of the granulosa. The further changes in the corpus luteum depend upon whether or not the ovum which was released is fertilized; if the ovum is fertilized, a *corpus luteum of pregnancy* develops, and if not it becomes a *corpus luteum of menstruation*. The follicular cells play a principal role in the formation of the corpus luteum. They divide and enlarge to form *granulosa lutein* cells. Simultaneously, the spindle-shaped cells of the theca interna penetrate radially into the follicular cells. Cells derived from the theca interna are called *theca lutein* cells. The corpus luteum of pregnancy grows larger than that of menstruation and does not undergo regression as soon. Its involution begins at about the fifth or sixth month of pregnancy. The remnant or scar of the corpus luteum which remains after regression is known as a *corpus albicans*.

Three tropic substances produced by the anterior lobe of the pituitary gland are concerned in the activity of the ovary, resulting in the production of two kinds of ovarian hormones: (1) FSH induces proliferation and maturation of the granulosa cells of the ovarian follicle; (2) LH acts subsequently to induce secretion by the granulosa and theca cells, and this secretion contains the estrogenic substances; (3) prolactin acts with LH to stimulate the growth of the corpus luteum from theca cells.

The follicular hormones. The estrogenic hormones found in the human are three in number. The most active, accounting for about 90 per cent of the activity of ovarian extracts, is *estradiol*. The other two active compounds are *estriol* and *estrone*. All of these compounds are steroids. The urinary excretion of estrogens increases rapidly in the early phase of the menstrual cycle to reach a peak at about the tenth day, then declines slightly and reaches a peak again at about the twenty-second day; then there is an abrupt falling off until the twenty-eighth day.

The actions of follicular hormones are remarkably selective, being substantially limited to the sex organs in primates. An excess of estrogen will produce marked effects upon the secondary sex organs. The oviducts show epithelial growth and there is an increase in their motility. The uterus increases in size and, generally, takes on the characteristics of the preovulatory uterus. The vaginal epithelium becomes more columnar, the Bartholin glands increase their secretory activity, and the breasts increase in size. A continuous administration of high dosages of follicular hormone results in interruption of the normal menstrual cycle. Immature or postmenopausal subjects or individuals who have had the ovaries removed are more sensitive to the action of the hormone than are normal adults.

The corpus luteum hormone. Following discharge of the ovum, the corpus luteum develops from granulosa cells and from cells of the theca interna. The former hypertrophy and become large, clear cells, while the latter migrate into the old follicular cavity, bringing a blood supply with them, and undergo a similar transformation. The cells become rich in a pigmented lipid substance which contains the characteristic hormonal product of the mature corpus luteum, *progesterone*. This substance has the same general steroid nucleus as the estrogens, androgens, and the adrenal cortical hormones. A lack of luteoid hormone may occur from failure of adequate corpus luteum formation following conception, or failure to maintain a formed corpus luteum. The uterine mucosa fails to be maintained in the progestational state and spontaneous abortion occurs. The presence of excessive amounts of progesterone may result either from administration of progesterone or from hemorrhagic lutein cysts. In the case of the latter, the principal effect is to delay menstruation, since the onset of menstrual bleeding seems to be related normally to the sudden drop in progesterone levels at about the twenty-sixth day of a normal cycle. The principal actions of progesterone are on the accessory sex organs, consisting of inhibition of motility of the oviducts, the production of the postovulatory type of uterine mucosal changes, and, in conjunction with estrogen, a proliferation of breast tissues.

Progesterone is excreted mainly as *pregnanediol*. The normal urinary excretion of pregnanediol is around five to ten milligrams per day. In pregnancy, it increases steeply from the third month to reach values around 70 to 80 milligrams per day at the time of parturition. The high levels are due primarily to production by the placenta with additional amounts coming from the corpus luteum and the adrenal cortex.

The Menstrual Cycle

In the human female, there are cyclic changes in the production of the two ovarian hormones and in the production of gonadotropins by the anterior pituitary. The cycle typically occupies about 28 days. In general, a sort of "balance and check" system exists between the anterior lobe of the pituitary and the ovaries. The gonadotropins stimulate the development and production of secretion by the follicle, and the corpus luteum and the hormones produced by these structures exert influences on production and release of gonadotropin by the anterior pituitary. Thus, the

sexual cycle is associated with, and dependent upon, complex cyclic changes in the production of four or five hormones.

The mucosal lining of the uterus is known as the *endometrium*. The condition of the endometrium is determined largely by the actions of the gonadotropic and ovarian hormones, and it is the cyclic variations in re-

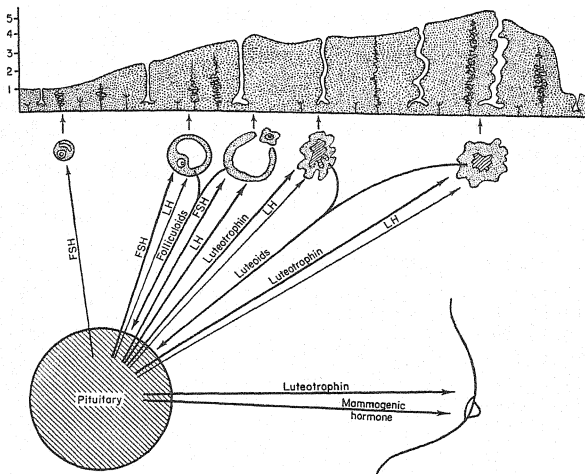


Figure 36-4. Hormonal influences concerned in the cyclic changes in the endometrium.

(From Youmans' *Basic Medical Physiology*.)

lease of these hormones which cause the periodic changes in the uterine mucosa. At one stage of the cycle, the endometrium breaks down and menstrual bleeding occurs. The endometrium is thinnest at the time of menstruation, and is gradually built up to become thickest again just before the next period of menstrual bleeding. The endometrium is characterized by the presence of numerous tortuous glands and minute coiled arteries. After the breakdown of the mucosa, only the basal portions of the glands remain and the epithelium is replaced by growth from these

remnants. During the time just after menstruation, a follicle is in the early stages of development and, typically, maturation of the follicle, with ovulation, occurs at a time about midway between the menstrual periods or ten to twelve days following the end of the preceding period in a twenty-eight-day cycle. Progesterone produced by the corpus luteum promotes the further development of the endometrium and makes it favorable for implantation of the fertilized ovum. If the ovum is fertilized and becomes implanted in the uterine mucosa, the corpus luteum continues to grow and its hormone is important in the maintenance of the endometrium in the early stages of pregnancy. If the ovum is not fertilized, the endometrium begins to undergo degenerative changes at a time about twenty-eight days from the onset of the preceding period of menstrual bleeding. These changes are shown diagrammatically in Figure 36-4.

Although the cyclic changes in production of estrogen, progesterone, and gonadotropins are responsible for the cyclic changes in the endometrium, it is difficult to obtain information concerning the amount of each hormone being secreted at each stage of the menstrual cycle. Apparently, estrogen secretion decreases sharply during the three or four days preceding the onset of menstrual bleeding; estrogen production is at its lowest level during menstruation and increases as the follicle develops during the next cycle to reach a peak level shortly before ovulation. Secretion of gonadotropin is considered to be highest during a six-day period which includes the time of ovulation. Progesterone production also shows fluctuations during the menstrual cycle.

Chapter 37

REPRODUCTION

Sex cells, or *gametes*, are produced by each of the two sexes, and, when male and female gametes unite, a fertilized egg, or *zygote*, is formed. The *zygote* is a single cell which develops into the new individual. The sex of the new individual is *determined* at the time of formation of the *zygote*, but the *differentiation* of sex is dependent upon the hormones produced in time by the testes and ovaries. If the ovaries or testes fail to develop, or are removed at an early stage in the growth of the organism, the typical sexual characteristics do not develop. Also, experiments may be performed on animals in which the ovaries are removed and testosterone injected. When this is done, male secondary sexual characteristics, both anatomical and physiological, are produced. Likewise, feminization of the male animal can be produced by the reverse procedure. Thus, the normal development of a person of a given sex is dependent upon the genetic factor, which is determined at the time of fertilization of the ovum, and upon the development and normal functioning of the corresponding sex gland.

Anatomy of the Sex Organs

Male. The principal features of the anatomy of the *male* sex organs are shown in Figure 37-1. The processes of spermatogenesis and oogenesis already have been described. The mature sperm cells are carried from the seminiferous tubules into larger tubules composing the epididymis (Figure 36-1) where they are retained while further ripening occurs. From the *epididymis*, a larger tube, the *vas deferens*, passes upward over the brim of the pelvis to enter the lower part of the abdomen. Small bodies, the seminal vesicles, are found on each side lying between the

remnants. During the time just after menstruation, a follicle is in the early stages of development and, typically, maturation of the follicle, with ovulation, occurs at a time about midway between the menstrual periods or ten to twelve days following the end of the preceding period in a twenty-eight-day cycle. Progesterone produced by the corpus luteum promotes the further development of the endometrium and makes it favorable for implantation of the fertilized ovum. If the ovum is fertilized and becomes implanted in the uterine mucosa, the corpus luteum continues to grow and its hormone is important in the maintenance of the endometrium in the early stages of pregnancy. If the ovum is not fertilized, the endometrium begins to undergo degenerative changes at a time about twenty-eight days from the onset of the preceding period of menstrual bleeding. These changes are shown diagrammatically in Figure 36-4.

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bladder and the rectum. They produce a secretion which is of importance in carrying and promoting the mobility of the sperm cells. A small duct connects each seminal vesicle with the corresponding vas deferens. The terminal portion of the vas deferens, or ejaculatory duct, and a portion of the urethra into which it empties are surrounded by a firm globular

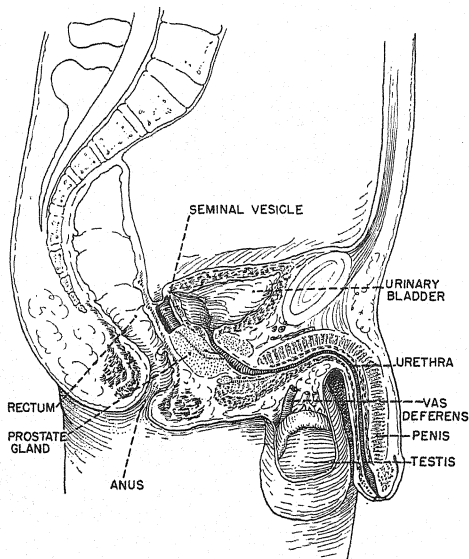


Figure 37-1. Male reproductive system.

Sagittal section.

mass, the prostate. The prostate contains numerous small glands which open into the urethra. The secretion from the prostate has functions similar to that of the seminal vesicles. The penis is composed of three columns of erectile tissue. The parallel paired two are anterior and the urethra is located centrally in the third.

Female. The anatomy of the *female* sex organs is shown in Figure 37-2. Two pairs of folds are found at the outlet of the vagina. The outer pair is the labia majora and the inner pair, the labia minora. A membrane, the hymen, extends between the inner pair and partially covers the

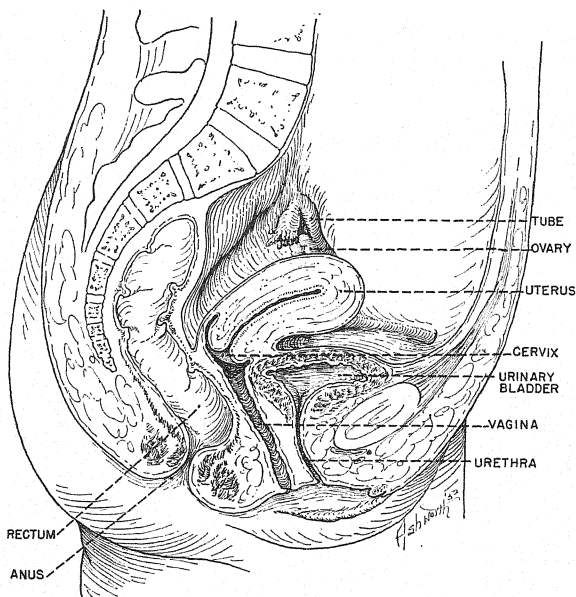


Figure 37-2. Female reproductive system.

Sagittal section.

vaginal outlet. The labia minora converge a short distance in front of the urethra and at this site the clitoris is located.

The vagina is a cavity extending four or five inches from the body surface to the lowermost portion of the uterus. The uterus is a firm organ

having the shape and size of a small pear. The rounded lower end (corresponding to the stem end of the pear) extends into the vagina. This portion is known as the cervix. The upper portion is the main body of the uterus (corpus). The uterus has a thick muscular wall and the uterine lining is the endometrium. The changes in the endometrium, and the structure of and production of ova by the ovaries already have been described. The oviducts, or fallopian tubes, are attached to the upper portions of the corpus of the uterus. They are shaped somewhat like trumpets which extend outward for a distance of two to three inches and partially enclose the ovaries. The terminal edge of the tube near the ovaries has finger-like projections which probably have a role in directing the released ovum into the end of the tube. The wall of the tube contains smooth muscle which shows rhythmic wave-like movements that help to propel the ovum toward the cavity of the uterus.

Spermatogenesis and Oögenesis

The production of sperm cells, or spermatozoa, occurs in the seminiferous tubules of the testis. The process is known as *spermatogenesis*. The primordial germ cells are seen in the most peripheral portion of a cross section of the tubule. They divide repeatedly to form *spermatogonia* which grow and divide to form primary *spermatocytes*. The latter undergo a type of division, known as *meiosis* or reduction division, by which cells are produced which have only half the number of chromosomes possessed by the parent cell. These cells, the *secondary spermatocytes*, divide into *spermatids* which mature into *spermatozoa*. Thus, mature sperm cells constantly are being produced and liberated into the lumen of the seminiferous tubule, and the earlier stages of development of sperm cells are seen as the periphery of the transected tubule is approached. This is illustrated in Figure 37-3.

The cells in the ovary which correspond to the spermatogonia in the testes are *oögonia*. During early development, they undergo successive division and growth; and, beginning at puberty, during each menstrual cycle, an oögonium develops into a *primary oöcyte*. The primary oöcyte, which is much larger than the corresponding primary spermatocyte, undergoes meiotic division to form a *secondary oöcyte* and a small cell called a polocyte. The secondary oöcyte divides to produce the *ovum* and

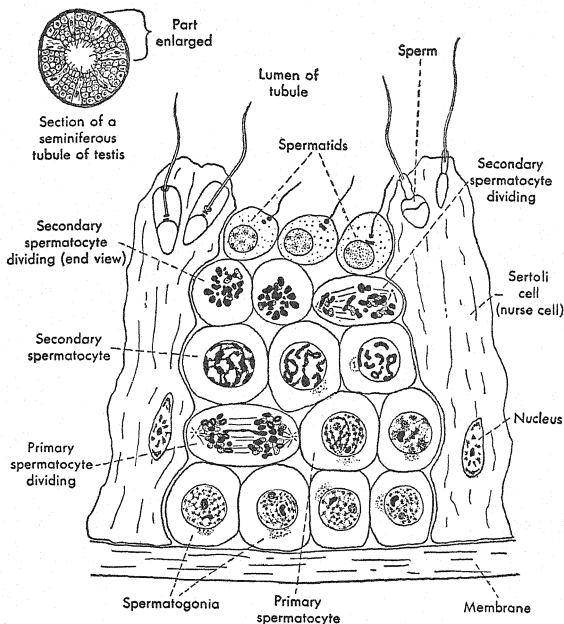


Figure 37-3. Diagram of a section of a seminiferous tubule showing the stages in spermatogenesis.

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a second polocyte. Thus, only one ovum is formed from each primary oöcyte, while four sperm cells are formed from each primary spermatocyte. The division of the primary oöcyte makes possible the reduction of the number of chromosomes in the ova to half the number in the oögonia. Then when the gametes unite, the zygote which is formed has the same

number of chromosomes found in all cells of the body. In Figure 37-4, the processes of spermatogenesis and oögenesis are illustrated to show the principal similarities and differences.

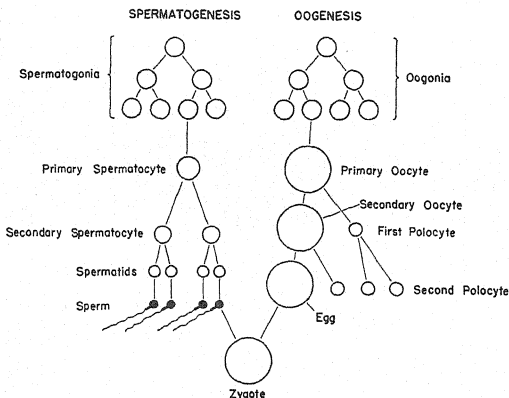


Figure 37-4. Diagram indicating the stages in spermatogenesis and oögenesis.

Coitus and Conception

Coitus is the act whereby the male deposits spermatozoa in the genital tract of the female. In most animals, there are periodic fluctuations in the urge to mate; but, in the human, periodicity is absent or ill-defined and psychic factors play a relatively important role. Basically, sexual desire is dependent upon influences exerted by the estrogenic and androgenic hormones in the female and male respectively. The physical responses in the human which precede coitus may result largely from psychic influence, and during coitus the psychic effects are supplemented by reflex influences. The essential phases of coitus are erection and ejaculation. *Erection* occurs as a consequence of distention of the venous sinuses of the penis with blood. The arteries supplying the erectile tissue of the penis dilate and veins draining this tissue are compressed. These changes are accomplished through the sacral division of the parasympathetic

system; activation of the sympathetic fibers from the lumbar region causes opposite changes. *Ejaculation* begins as propulsive waves of contraction of the smooth muscle layers of the vas deferens and of smooth muscle in the seminal vesicles and prostate. In the completion of ejaculation, waves of contraction pass over the striated muscles of the perineum, and the

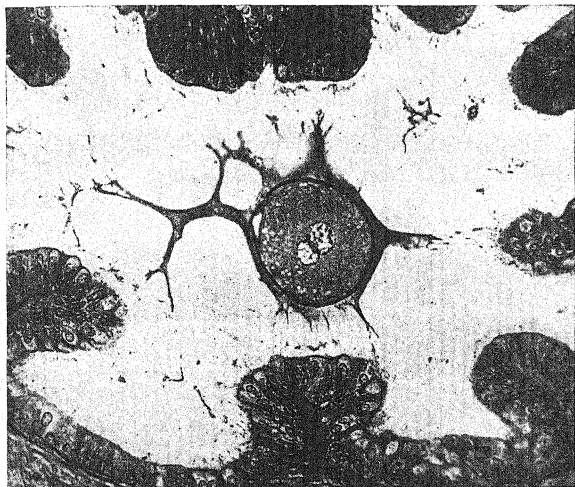


Figure 37-5. Pronuclear stage of fertilization.

This is a photomicrograph of a section of the ampulla of the oviduct of a red squirrel. The epithelial lining of the ampulla is seen around the border of the figure. The sperm has entered the ovum and the nucleus of the sperm has approached the nucleus of the ovum. Magnification is 300 times. (Courtesy of H. W. Mossman.)

semen is ejected from the urethra. In the female, erectile tissue in the vulva and vagina becomes engorged during coitus, and the Bartholin glands secrete into the posterior part of the labia majora.

The spermatozoa are deposited near the cervix, and propel themselves by spiral movements. They make their way into the uterus and out into the fallopian tubes where, generally, the ovum is fertilized.

Embryology and Gestation

(Embryology is the study of the development of the organism from the time of fertilization until the body and organs assume a form similar to that which is found in the adult. In the case of the human, all of these changes occur *in utero*.)

Fertilization and the segmentation which occurs initially have been described. (By the fourth day after fertilization, the *free blastocyst* has developed. This is a hollow sphere, the wall of which is composed of one

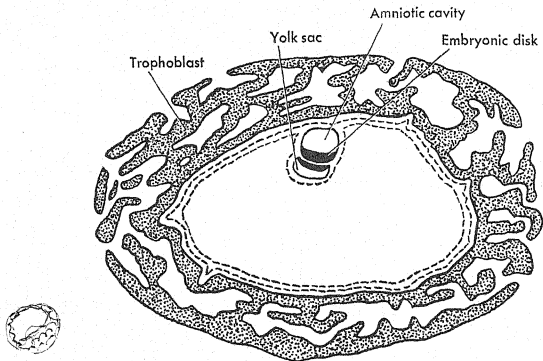


Figure 37-6. Diagram of section through an early embryonic disk and chorionic sac.

layer of cells with an embryonic knot, or *inner cell mass*, at one pole. The inner cell mass develops into the embryo which is nourished by substances which diffuse through the trophoblast (see Figure 37-6). The blastocyst reaches the cavity of the uterus on the fourth to fifth day. In the meantime, under the influence of the corpus luteum, the uterine lining has undergone transformations which are favorable for implantation. (The zona pellucida ruptures and the trophoblast becomes attached to the uterine lining, then the blastocyst burrows in and becomes enclosed in the uterine lining.) The stage of implantation begins at 4½ to 7 days after fertilization and is well advanced by the twelfth day. (Next, projections,

secreted
memb.
around
the
ovum
(by
follicle
cells)

known as primitive *villi*, develop on the outside of the trophoblast. These serve to increase the surface area and hence provide for absorption of nutrients. The villi become complicated in form and develop blood vessels which connect with those of the embryo.)

(The inner cell mass develops into a flattened, pear-shaped disk; two cavities, the *yolk sac* and *amniotic cavity*, appear within the blastocyst (Figure 37-7). The *germinal disk* composed of two layers of cells lies between the two cavities. The layer on the floor of the amniotic cavity is

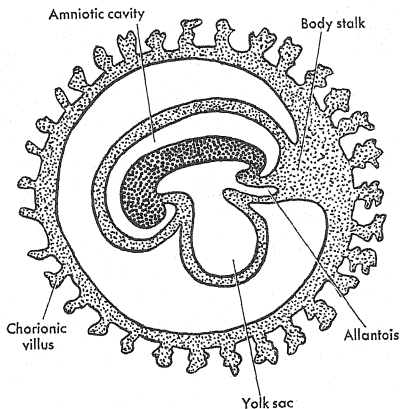


Figure 37-7. Diagram of section through a young embryo showing membranes and body stalk.

the *ectodermal* layer and that next to the yolk sac is the *endodermal* layer. A third layer, the *mesodermal*, appears later between the other two. These are the three germ layers from which all of the tissues of the body develop.

If one should look into the opened amniotic cavity of a human embryo which is about 16 days old (as shown in Figure 37-8), he would see the upper ectodermal surface of the pear-shaped disk. The broad portion is the head end and a groove is seen extending along the disk dividing it into symmetrical halves. This is called the *neural groove*, since it develops into

the brain and spinal cord.) A small node, first described by Hensen, is present at the caudal end of the neural groove. A column of cells originates close to this node and burrows forward beneath the neural groove towards the head end of the disk. This is the *notochordal process* and marks the earliest stage in development of the vertebral column. It will be remembered that the possession of a notochord at some stage in life is the basis

for classifying an animal as a Chordate.) In amphioxus, one of the lower Chordates, the notochord remains in the mature organism as a flexible elastic rod.

The notochord elongates and mesodermal cells lie on each side of it. The mesoderm becomes segmented into a series of somites. The segmentation begins at the head and progresses until 44 somites are formed. The segmentation is reflected in the arrangement of ribs, vertebrae, intercostal nerves, and skin segments supplied by them in the region of the trunk. In other parts of the body, the basic pattern becomes greatly modified.

Another change in the mesoderm involves a splitting of the outer edge so that it becomes divided into two layers. The upper layer comes to lie on the inner side of the ectoderm, and the lower layer becomes applied to the endoderm. Thus, a cavity, the *celom*, is left between the two layers

on each side of the germinal disk. The celomic cavity subsequently becomes subdivided into the main body cavities. The developing organs become invaginated, in effect, into a double-layered sac. This explains the double layer that covers the internal organs (visceral and parietal layers of pericardium, peritoneum, and pleura). The mesentery of the bowel is formed by the two layers in apposition as they pass from the viscus to their dorsal attachment.

Folding processes result in the embryo rising up in the amniotic cavity.

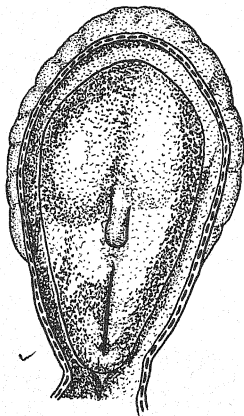


Figure 37-8. Drawing of human embryonic disk about 16 days old. Viewed from above with membranes cut away. About 40 times actual size.

The amnion is swept round until it surrounds a stalk, the umbilical cord, left between the embryo and the placenta. The embryo becomes curled up as it develops more rapidly than the amniotic cavity enlarges. When the embryo is 24 days old, it measures about 2.5 to 3.0 mm. in length from crown to rump.

A series of pharyngeal arches and clefts develop on each side of the primitive mouth cavity. Derivatives of these ultimately develop into structures in the face, jaws, ears, tongue, larynx, and the endocrine glands in the neck.

During the period from 3 to 7 weeks, the organ systems develop. Externally, at 28 days, arm and leg buds have just formed. At 30 days, the ears and eyes are defined. Parts become progressively more apparent until at 8 weeks the embryo has an unmistakably human appearance, as indicated by the relatively large size of the brain.

The term fetus is used to refer to an embryo when it has acquired all of the characteristics that can be recognized in later life. This stage is reached by the end of the second month. The fetal period is mainly one of growth and alterations in shape and proportion. The membrane immediately surrounding the fetus is the *amnion* and the closed space or cavity formed by it is filled with *amniotic fluid*. The other membranes, *chorion* and *allantois*, are illustrated in Figure 37-9. The amniotic fluid acts as a protective cushion and permits some motion of the fetus. The amniotic membrane may rupture several days before the birth of the child; however, normally, it ruptures during birth. Occasionally, it remains intact so that it still envelops the head as it emerges from the birth canal.)

The fetus is connected to the uterine wall by means of the umbilical cord which contains the blood vessels that are concerned with carrying nourishment to the fetus and with transporting wastes from the fetus to the mother. The umbilical cord connects with the placenta. The part of the uterine wall which enters into the formation of the placenta is a mass of spongy tissue filled with blood coming from the mother's blood stream. The portion of the placenta derived from the embryo, the chorion, gives rise to numerous *villi*, which project into the maternal portion of the placenta. The blood of the fetus circulating in the capillaries of the chorionic villi is separated from the blood of the mother by cellular layers sufficiently thin to allow diffusion of substances between the maternal and fetal circulation, much as the interchange which occurs between blood plasma and the interstitial fluid. There is no mixing of fetal and maternal blood in the placenta.)

(In addition to being the site of exchange of substances between the mother and fetus, the placenta also functions as an endocrine gland producing hormones necessary for the continuation of pregnancy. The placenta produces estrogens, small amounts of progesterone, and a substance similar to the luteinizing hormone of the anterior pituitary.) The latter is

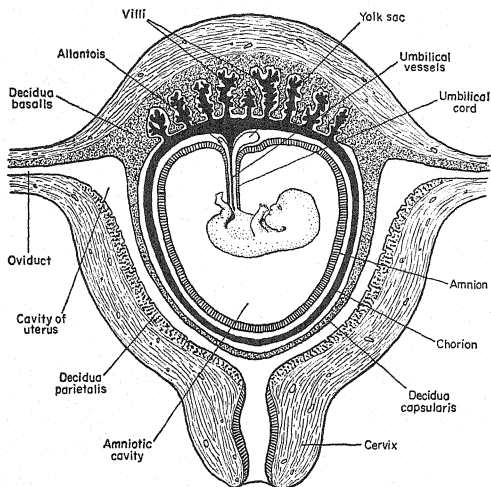


Figure 37-9. Sectional view of pregnant uterus showing fetal membranes.

(By permission after Huettnner, *Comparative Embryology of Vertebrates*. Copyright, 1941, by The Macmillan Company.)

known as *chorionic gonadotropin*. The activity of the corpus luteum of pregnancy is maintained after its involution by the humoral influences from the placenta; hence in the latter stages, pregnancy may continue after removal of the ovaries.

Beginning early in pregnancy, considerable amounts of chorionic gonadotropin are excreted in the urine and this provides a basis for some of the pregnancy tests. Small amounts of urine from a pregnant woman

when injected into a non-pregnant female rabbit or rat rapidly produce characteristic changes in the animal's ovaries.

Parturition

The act of giving birth to the child is known as *parturition*. The cause of the onset of labor after about 40 weeks of gestation is not known; however, it has been postulated that oxytocic substances from the posterior pituitary are liberated into the blood in larger amounts at this time.

During labor, the hypertrophied uterine musculature undergoes powerful periodic contractions. These occur at first infrequently and then steadily become more closely spaced, so that the intervals between contractions may ultimately be only two or three minutes in duration. In most instances, the position of the fetus at the time of labor is such that the crown of the head is at the cervix, and as labor progresses the cervix becomes thinned out and steadily dilates as the head is forced against it. If the "presenting" part of the fetus is not the head, labor is apt to be more difficult than if the fetus were in this position. The birth canal is so constructed that the fetus is expelled most readily if the head can serve as a wedge to dilate the cervix (Figure 37-10). Also, as illustrated, it is most common for the occiput to present in the anterior position; therefore, with the mother in the usual position for delivery, the infant's face is downward as the head emerges from the birth canal.

When the cervix has become dilated sufficiently to let the head of the fetus pass through into the vagina, reflexes are elicited which promote contraction of the musculature of the abdomen and the diaphragm, and these reflex contractions are supplemented by voluntary effort. The fetus is expelled by the uterine contractions and by the action of the muscles which on contraction increase the intra-abdominal pressure. There is great variability in the duration of labor depending especially upon whether it is the first pregnancy (primipara), the position of the fetus, and the comparative sizes of the infant and the birth canal. The duration of labor tends to become shorter with successive pregnancies.

Lactation

The mammary glands enlarge during pregnancy under the influence of estrogen and progesterone. The sudden onset of lactation after parturition probably is due in part to the sudden decrease in production of estrogen

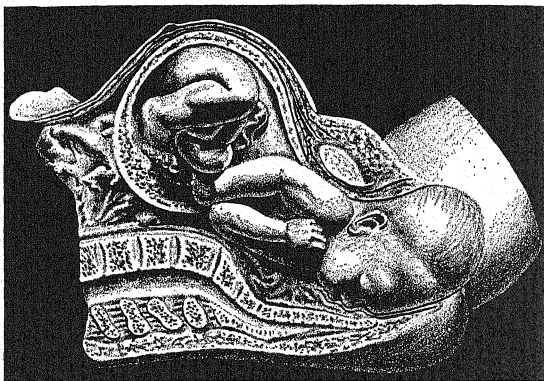


Figure 37-10. The process of birth.

Upper figure, head passing through the dilated cervix of the uterus into the upper end of the vagina. *Lower figure*, head passing through the opening of the vagina. (By permission after Patten, *Human Embryology*. Copyright, 1946, by The Blakiston Co., and by courtesy of the Cleveland Health Museum.)

which, though it has a stimulating effect on the development of the mammary gland, has an inhibitory effect on lactation. At the same time, the anterior pituitary is released from inhibitory influences and liberates more prolactin. If it is necessary to suppress lactation after the birth of a child, this result can be achieved by administration of either natural or synthetic estrogens. Once lactation begins after parturition, its continuation is stimulated by the emptying of the mammary glands and by the mechanical stimuli associated with nursing.

The similarities and differences in the percentage composition of human milk and cow's milk are shown in the table.

	WATER	PROTEIN	FAT	LACTOSE	MINERALS	CAL./LB.
Human milk	87.5	1.4	3.7	7.2	0.2	307.
Cow's milk	87.1	3.4	3.9	4.9	0.7	310.

The Fetal Circulation

The fetal circulation differs markedly from that of the infant. In the infant after birth, it is necessary for the blood to be pumped through the pulmonary circuit to obtain its oxygen and give off carbon dioxide and to flow to the vessels of the digestive tract to obtain nutrients. In the fetus, the lungs and the alimentary tract are functionless since the exchange of oxygen, carbon dioxide, and nutrients occurs in the placenta. The lungs are shunted out of the circulation in the fetus as follows. Oxygenated blood flows to the fetus from the placenta by the umbilical vein (Figure 37-11). It mixes with venous blood from the legs of the fetus and reaches the heart by the inferior vena cava, then it is deflected through the *foramen ovale* from the right atrium into the left atrium. It passes from the left atrium to the left ventricle to be pumped into the systemic circuit which includes the umbilical arteries carrying blood to the chorionic villi. Some of the blood which enters the right ventricle from the right atrium is shunted from the pulmonary artery by the *ductus arteriosus* to the aorta. Thus, the lungs are by-passed by two shunts: right atrium to left atrium by the *foramen ovale*, and pulmonary artery to aorta by the *ductus arteriosus*. At birth, normally, the *foramen ovale* and *ductus arteriosus* close, and all of the blood which is returned to the right heart is pumped to the lungs. These changes are probably related to changes in

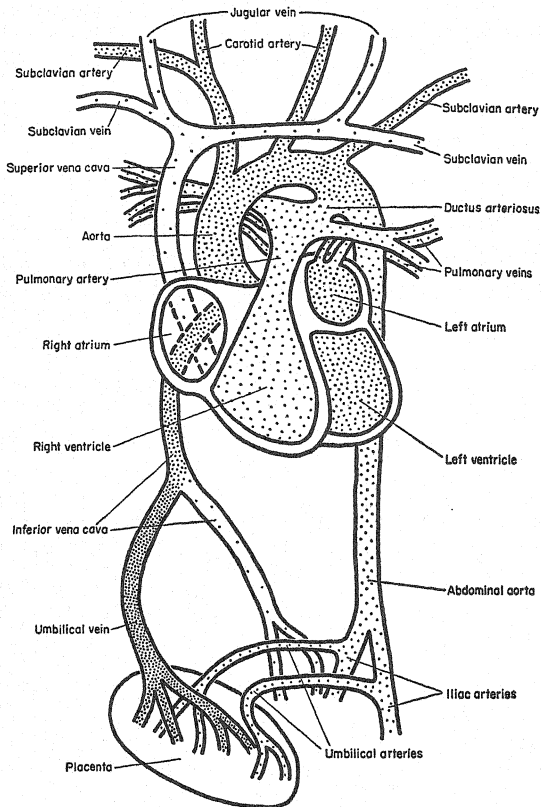


Figure 37-11. Diagram of the fetal circulation.

Relative concentration of oxygen is indicated by density of stippling. The highest oxygen tension is found in the blood of the umbilical vein. (By permission from Lee, *Physiology of Tissues and Organs*, Charles C Thomas Publishers, 1950.)

pressure in the pulmonary circuit resulting from a sudden decrease in resistance to blood flow in the lungs produced by expansion of the chest when breathing begins. In some cases, one or both of these communications persist and characteristic signs and symptoms are produced.

Multiple Births

Multiple births occur at different frequencies in different countries and races. In American whites, according to Nicolas and Hall (1942), twins occur once in 87 confinements, triplets once in 87² confinements, and quadruplets once in 87³ confinements. Apparently, six is the largest number of births resulting from a single confinement.

There are two types of twins: True twins (identical, monozygotic) and false twins (fraternal, dizygotic). False twins result from the development of two eggs discharged from separate follicles, fertilized by different sperms, and implanted individually in the uterus, hence each member of the pair has its individual chorion and placenta. The individuals may be of the same or opposite sex and they have a degree of family resemblance such as occurs in brothers and sisters of different ages.

True or identical twins are derived from a single egg, hence they have the same genetic background. They always are of the same sex and are strikingly similar in appearance. Human identical twins develop within a common chorionic sac and have a common placenta. The umbilical cords, however, usually are separate.

Triplets, quadruplets, etc., may be all identical or they may be a mixture of identical and fraternal individuals. Approximately one third of American twins are of the monozygotic type, while in some other countries the frequency of this type is said to be considerably higher. Multiple ovulation, and hence the birth of ordinary twins, tends to run in some family lines, and it is possible that the same is true of the tendency to give birth to true twins.

Monozygotic twins have been studied extensively in an attempt to determine what traits and diseases or abnormalities have an hereditary basis. Since true twins have an identical chromosomal makeup, unless the chromosomes become altered after conception, those characteristics which have a strictly hereditary basis should appear in both members of the pair. Usually twins are reared in the same environment; however, in a few instances this has not been the case. A comparison of the traits of

identical twins reared in different environments obviously is of particular interest to anatomists, physiologists, and psychologists.

The blood groups, according to H. H. Newman, may be presented as examples of fully hereditary characters in that identical twins always belong to the same groups. The color of the hair and eyes is determined by heredity also, but may show slight modifications as a result of effects of environment. Monozygotic twins reared apart, on the average, were found to be no more different in measurable physical characters than such twins reared together except for one character, body weight; however, where mental traits of monozygotic twins reared apart were compared with those of monozygotic twins reared together, significantly greater differences in the former group than in the latter were observed. Those reared apart showed greater differences in intelligence quotient (I.Q.), scholastic achievement, and personality.

Chapter 38

REGULATION OF VISCERAL FUNCTIONS

Centers in the Medulla

The medulla oblongata contains several centers which integrate the activity of visceral effector cells. In general, the medullary centers respond (1) to impulses arriving over afferent pathways, (2) to impulses conducted down to them from higher regulatory centers, particularly in the hypothalamus, and (3) to changes in the composition of the blood reaching the centers. The latter is true especially for the respiratory center and the vasoconstrictor center which are quite sensitive to alterations in the carbon dioxide tension of the blood.

The details concerning neural regulation of circulation and the control of respiration have been presented in other sections. It will be recalled that these functions are controlled largely by means of the centers located in the medulla oblongata. Blood pressure and heart rate are regulated by the vasoconstrictor, vasodilator, cardioinhibitory, and cardioaccelerator centers and respiration by the inspiratory and expiratory centers, and the pneumotaxic center located at the level of the pons. Each of these centers actually consists of two half-centers, one being located on each side of the midsagittal plane. The centers which have opposite actions on a given effector, for example, the cardioinhibitory and cardioaccelerator centers, commonly are reciprocally influenced.

The level of activity in a given visceral efferent pathway at any instant or, in other words, the frequency at which impulses are set up, is the resultant of numerous simultaneous influences on the medullary centers. Some of these influences are such as to produce an increased activity in the pathway, while some serve to cause a decreased activity. For example, the vasoconstrictor nerves provide the final common path for influences from changes in pressure in the carotid sinuses, lowering of the oxygen

tension in the carotid bodies, cooling of the skin, changes in carbon dioxide tension in the vasoconstrictor center, changes in temperature of the blood flowing through the hypothalamus, etc., hence caliber of the arterioles at a given moment represents the resultant of all of these influences as well as, in addition, the local influences exerted by carbon dioxide tension, oxygen tension, and hydrogen ion concentration.

Certain types of activity which are integrated through the centers in the medulla involve coordinated responses of skeletal musculature as well as responses of visceral effector cells. This is true, for example, for respiration and vomiting. That such activities are adequately coordinated at the level of the medulla oblongata is evident from the fact that the animal is still capable of performing them when the brain stem is transected above the medullary level. However, other processes which, for the most part, are somewhat more complex but which depend in large degree upon the activity of the autonomic system are integrated from still higher levels in the brain stem. These higher autonomic centers are located mainly in the hypothalamus. Visceral functions and metabolism are controlled both by the autonomic system and by the endocrine glands; the hypothalamus is the principal center for integration of the neural influences, and the anterior portion of the pituitary gland produces hormones which control most of the endocrine glands (page 390). Thus, there are located in proximity to each other at the base of the brain in a relatively small area the most important neural and hormonal mechanisms for control of visceral functions.

Functions of the Hypothalamus

The hypothalamus is located in the ventral part of the brain. The hypophysis is connected with the lowermost portion of the hypothalamus by a narrow stalk as shown in Figure 38-1. The relation of the hypothalamus to visceral effectors has been shown largely by observing the effects of direct electrical stimulation, by "release" of the hypothalamus following section of its connections with higher centers, and by effects of lesions of the hypothalamus itself. Stimulation of the hypothalamus causes immediate responses in a number of visceral effectors, whereas similar stimulation of most of the other parts of the brain does not elicit such responses. It appears that certain of the hypothalamic nuclei are concerned primarily with influencing the adrenergic part of the auto-

nomic system, whereas other nuclei control mainly cholinergic pathways. In general, stimulation of the posterior and lateral hypothalamic nuclei causes cardiac acceleration, elevation of blood pressure, dilatation of the pupil, retraction of the nictitating membrane (the "third eyelid") in carnivores, and inhibition of intestinal motility. In this case, liberation of epinephrine from the adrenal medulla occurs also and, after a latent period, supplements the actions of the adrenergic nerves. Cholinergic

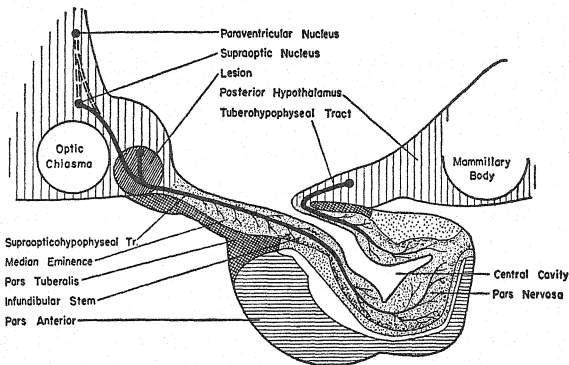


Figure 38-1. Diagram of a midsagittal section through the hypothalamus and hypophysis of the cat.

The circle filled with oblique lines indicates the site of a typical lesion which produces diabetes insipidus. (After C. Fisher *et al.*, *Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance*. Copyright, 1938, by S. W. Ranson.)

effects are more apt to be evoked during stimulation of the anterior and middle group of nuclei; typically, the urinary bladder contracts, heart rate decreases, and there is increased gastrointestinal motility, sweating, and vasodilatation. However, results obtained from stimulation of a given site differ with variations in the intensity and frequency of stimulation.

Localized lesions of the hypothalamus cause striking changes in visceral functions. These include decreased metabolism, lethargy, hyperglycemia, gastric disturbances, impairment of heat regulation, metabolic disturbances, and *diabetes insipidus* (page 382).

Emotional Expression

Strong emotions are accompanied by striking changes in the activity of many organs and tissues which are innervated by the autonomic nervous system, and at the same time, involuntary alterations in the activity of skeletal muscle are produced. For example, if a cat is confronted with a barking dog, the cat's pupils become dilated, the nictitating membrane is retracted, the heart rate is increased, the hair on the back "stands up," and the back is arched. The visceral responses observed in fear and rage are integrated through the hypothalamus. Such reactions normally are held in check by impulses reaching the hypothalamus from higher portions of the brain. In animals which have had the cerebral hemispheres removed, the characteristic "rage" response not only is still possible, but is more readily set off. The reaction in such animals is known as *sham rage*. It consists of widespread activation of the sympathetic nervous system, liberation of epinephrine from the adrenal medullae, and skeletal muscular activity (biting, clawing, lashing of the tail). Direct stimulation of certain portions of the hypothalamus may set off "sham rage" and suitable lesions of the hypothalamus prevent the response. In the earlier studies, predisposition to sham rage was produced by removal of the entire cerebral cortex. However, later studies have shown that only localized portions of the cortex need be removed to "release" the hypothalamus, and removal of certain other cortical areas actually may make the animal more placid than before the operation.

Autonomic representation in the cerebral cortex. The hypothalamus has connections with nuclei of the thalamus which in turn project to the orbitofrontal portion of the cerebral cortex. Bilateral destruction of this part of the cerebral cortex causes autonomic disturbances and a rise in the threshold for visceral pain. Electrical stimulation of specific areas of the cerebral cortex (particularly 4, 6, and parts of 8) produces changes in blood pressure and heart rate, sweating, piloerection, alteration of gastric motility, lacrimation, salivation, etc. Responses of the intrinsic eye muscles have been produced by stimulation of Areas 8 and 19.

Heat Regulation

Fish, amphibians, and reptiles show changes in body temperature in the same direction as changes in the environmental temperature. Birds

and mammals, on the other hand, have a relatively high body temperature which is maintained at a remarkably constant level in the presence of wide changes in the temperature of the environment and changes in the rate of heat production by the body. The former classes of vertebrates are said to be cold-blooded and the latter, warm-blooded; however, *poikilothermic* (variable temperature) and *homothermic* (constant temperature) respectively are terms which more accurately designate the two types.

The maintenance of a constant body temperature is possible only if rate of heat loss and rate of heat production are exactly balanced. The rate of heat production above the basal level, as described in the chapter on metabolism, is related chiefly to the activity of skeletal muscle. The regulation of the rate of loss of heat from the body to the surrounding air will be influenced greatly by the temperature of the air, and this can vary during the year by as much as 160°F. The rate of loss of heat from the body is determined by radiation, convection, conduction, and evaporation of sweat. The first three of these processes determine the rate of heat loss from an inanimate object, the last is peculiar to the living organism. However, there are other processes peculiar to the organism that can influence the rate of loss of heat by radiation, conduction, and convection. Radiation refers to the passage of heat waves from a warm object to a cooler object; conduction is the transfer of heat between contiguous media (or between portions of the same medium) as from the skin surface to cooler air or water which is in contact with the skin. Convection refers to currents in the medium. For example, if air is still, the air which has been warmed by the body by conduction will in turn lose heat to the adjacent air by conduction so that the air temperature near the body is higher than the temperature of the air farther away. Therefore, the difference or gradient in temperature between the skin and the adjacent air will be lowered and rate of heat loss decreased. On the other hand, if the warm air near the body is removed by convection currents and replaced by cooler air, the heat gradient from skin surface to the adjacent air will be greater and heat loss will be accelerated.

The mechanisms for maintaining the body temperature relatively constant at 98.6°F. can best be described by considering separately the responses of the body which are observed when it is subjected on the one hand to low temperatures and on the other hand to high temperatures. In the former case, the mechanisms available for opposing a fall in body temperature become evident, and in the latter case, the mechanisms for preventing a rise in body temperature are active.

Response to cold. When a lightly clad subject is placed in a room at a temperature of, for example, 20°F ., heat is lost rapidly by radiation, convection, and conduction. One of the first bodily reactions to the low environmental temperature is constriction of arterioles in the skin, especially in the hands and feet, so that the temperature of the body surface decreases, and this tends to decrease the rate of heat loss. However, conservation of the heat being produced by the body under near-basal conditions is not sufficient to maintain the temperature under these circumstances. Increased heat production also is necessary, and this is achieved either by shivering or by voluntary use of skeletal muscle. If the environmental temperature is very low, the body temperature will decrease in spite of both vasoconstriction and shivering. Piloerection is an important additional heat conserving mechanism in carnivores, but is of no importance in man.

Response to heat. When the temperature of the surrounding air moderately exceeds the temperature of the body, for example, 110°F ., not only can no loss of heat from the body occur by radiation, conduction, or convection, but heat is absorbed as a result of these processes. Hence heat loss becomes dependent entirely upon perspiration and evaporation of sweat. The vaporization of each cubic centimeter of water involves the uptake of a specific amount of heat; if sweat drips from the body instead of evaporating, it has no cooling effect. The rate of evaporation of sweat from the surface of the body is faster, the lower the water vapor tension, or humidity, of the surrounding air. If the air is already saturated with water vapor, the sweat will not evaporate, but will run from the surface of the body. At high environmental temperatures, if either sweating or evaporation of sweat is prevented, the body temperature inevitably will increase, since no mechanism for heat loss remains.

At ordinary comfortable room temperatures, it appears that regulation of heat loss in the resting or sedentary individual is accomplished mainly by regulation of blood flow through the skin. An increase in room temperature of a few degrees will elicit a considerable rise in the temperature of the skin of the hands, while a slight decrease in room temperature will cause a considerable reduction in skin temperature.

Heat-regulating center. The changes which occur in response to a rise or a fall in environmental temperature, since they include vasomotor activity and sweating, involve activation of the autonomic nervous system. In addition, the skeletal musculature is utilized. In animals with a hairy coat, piloerection is important for heat conservation and, in dogs, panting

occurs to accelerate heat loss by evaporation of water from the respiratory tree and mouth. These complex adjustments and responses are dependent upon the hypothalamus which is the primary center for heat regulation. Destruction of the hypothalamus or of its efferent connections with the spinal cord, or administration of drugs which impair the functioning of the hypothalamus, causes the mammal to become more like the poikilothermic animals; the temperature of the body varies readily with changes in the temperature of the environment.

The sweating and vasodilatation that occur in response to a warm environment are elicited reflexly from the rise in skin temperature and, secondly, as a result of a slight increase in the temperature of the blood flowing through the hypothalamus. Vasoconstriction, piloerection, and shivering likewise are elicited reflexly from a decrease in skin temperature and by a decrease in the temperature of the blood reaching the hypothalamus.

Fever. A rise in body temperature, or *fever*, is characteristic of a large number of diseases caused by microorganisms. In fever, the increase in heat production is only a fraction of that produced by moderate exercise; therefore, the increase in body temperature is not based on overtaxing the mechanism for heat loss. In explaining fever, one may consider the hypothalamic heat-regulating center to be analogous to a thermostat, and may assume simply that the thermostat is set for a higher temperature as a result of the action of products of the infecting organisms. It appears that in some instances the thermostat may be set suddenly for a higher temperature, hence the body is faced with the necessity of conserving and producing heat until the body temperature is elevated to this higher level. The skin vessels constrict, lowering the skin temperature and causing the patient to feel cold, and at the same time severe shivering is induced. The "chill" which results signifies a rising body temperature. On the other hand, if the thermostat is suddenly set back to normal, say by the quick disappearance of the infectious agent, sweating and vasodilatation are produced. Thus, paradoxically, when the patient feels cold his temperature is rising and when he feels hot his temperature is falling.

Sleep and Arousal

Certain forms of encephalitis which lead to damage of structures deep in the brain may result in so-called "sleeping sickness." In other words, the

patient cannot be aroused. Hence it is apparent that the activity of parts of the brain (lying in part in the hypothalamus) are essential for the waking or conscious state. It has been known for a long time that the hypothalamus contains centers which, on electrical stimulation, will promote arousal; and some investigators, including W. R. Hess, have reported that sleep may be produced by hypothalamic stimulation. The tendency at present is to consider that the important mechanism in the hypothalamus is a *waking* center and that sleep simply is the result of inactivity of the waking center (Lindsley). Lindsley suggests that the electrical stimulation which was described by Hess as causing sleep actually may have done so by blocking the conduction of impulses to a waking center.

A major recent contribution to the knowledge of arousal is that of Magoun and associates who demonstrated that the stimulation of portions of the reticular formation in the brain stem results in arousal. This has been called the ascending reticular activating system. It is well known that impulses conducted to the brain over the major afferent systems tend to cause arousal, but the system described by Magoun as also being concerned with walking is more diffuse and indirect.

The work of students of sleep and arousal has been facilitated as a result of the discovery that the electroencephalogram (EEG) shows a characteristic pattern in the sleeping animal and this pattern changes abruptly when the animal is aroused. The EEG in sleep is characterized by slow waves of large amplitude and on arousal it shows a sudden shift to fast waves of low amplitude. Stimulation of the ascending reticular activating system causes the latter changes in the EEG at the same time that it causes the animal to awake as judged from its behavior. There have been enough experiments performed showing the simultaneous alerting of the animal and the characteristic EEG changes to allow the use of the EEG as an index of arousal.

Any lack of awareness of surroundings is included under the heading, unconsciousness. However, although unconsciousness accompanies normal sleep it can result from many other causes such as anoxia, hypoglycemia, acidosis, a severe blow on the head, anesthesia, etc. The most severe degree of unconsciousness is known as coma. In this condition the patient cannot be aroused by sensory stimuli. Arousal of a person in coma usually depends upon removal of the specific cause, whether it be hypoglycemia, anoxia, or elimination from the body of an anesthetic agent.

There are also varying degrees of consciousness ranging from barely awake through a state of alertness to arousal of an extreme degree, or excitement, which involves the liberation of epinephrine and the mobilization of reserves for physical activity (see page 403). Lindsley tabulates a full range of EEG stages against a behavior continuum and corresponding states of behavioral efficiency. He writes: "It should be noted that the most aroused or excited state behaviorally is represented by a low-voltage fast EEG picture, and is paralleled by poor attention and behavioral inefficiency. On the other hand a slightly less activated state, corresponding to alert attentiveness, favors selective and shifting attention, and behavioral efficiency." The sequence of changes in the order of increasing activity of the waking mechanism may be listed as (1) relaxed wakefulness, (2) alert attentiveness, (3) excitement. In the first two stages, there is good behavioral efficiency and in the third, there is lack of control and sometimes "freezing up."

Chapter 39

MECHANISMS OF INHERITANCE

Physical Basis of Heredity

The science which deals with the phenomena of heredity is known as *genetics*. The term is derived from the *genes* which are present in the chromosomes. The chromatin of the nucleus is gathered into chromosomes which are distinctly visible as discrete bodies only during cell division. Each species of organism has a specific number of chromosomes; the number in man being 46. There are 23 pairs. Under favorable conditions, the members of each pair are sufficiently distinct in shape or size to be identified on microscopic examination. In mitosis, each of the two daughter cells receives the same number and same kind of chromosomes that were present in the parent cell. Before division of the cell, each chromosome produces a replica of itself; a line of cleavage forms longitudinally and the chromosome appears to split. Then for a time, until the division of the cell is completed, the cell contains 92 chromosomes, and again, when the division is completed, each daughter cell contains 46. In meiosis, which occurs in the processes of oögenesis and spermatogenesis, instead of 23 pairs of chromosomes appearing in each daughter cell, one of each pair goes to each cell, so that each gamete contains only one of each kind of chromosome, that is, one set of 23 chromosomes. When the gametes unite, the zygote which is formed contains 23 pairs. Thus, the fertilized ovum gets one of each pair of chromosomes from each parent.

Genetic Determination of Sex

There is one exception to the rule that the two members of a pair of chromosomes are similar to each other in size and shape. In females, there

are two identical so-called *sex chromosomes*, each of which is designated by X. In males, one member of the pair of sex chromosomes is similar to the sex chromosomes seen in the female and hence is designated X, but the other member of the pair is smaller and is known as the Y chromosome. Thus, in addition to the other 22 pairs of chromosomes, men have an X and a Y chromosome, and women have two X chromosomes. Whether the new individual is to be a male or a female is determined by whether there are one or two X chromosomes present when the zygote is formed.

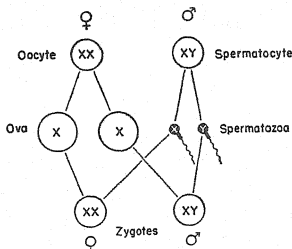


Figure 39-1. Genetic basis for determination of sex.

Since the female has only X chromosomes, each ovum will receive an X chromosome. On reduction division in spermatogenesis, however, half of the sperm cells will receive the X chromosome of the pair and the other half will receive the Y chromosome. The fertilization of an ovum by an X-bearing sperm will result in an XX (female) combination in the zygote, while fertilization of an ovum by a Y-bearing sperm will result in an XY (male) combination in the zygote. Since equal numbers of X-bearing and Y-bearing sperm cells are produced, on this criterion alone one would expect that equal numbers of each type of zygote would be formed, and hence equal numbers of each sex would be born. However, this is not so; more boys are conceived than girls, and about 107 viable males are born per 100 females. The difference in numbers conceived has been explained by the hypothesis that the Y-bearing sperm, having a lighter load to carry, will win the race to the ovum in slightly more than half of the cases.

Mendelian Inheritance

The genes exist in pairs called *allelomorphs*, one member of which is contributed by each parent. The two genes composing the allelomorphic pair may be either similar or dissimilar. The individual possessing the former is said to be *homozygous* with reference to the trait determined by that particular pair of genes, while an individual possessing a dissimilar pair is *heterozygous*.

Due to the process of reduction division (page 419), the gametes possess only half of the number of chromosomes found in the cells of the other parts of the body. When fertilization occurs, 23 chromosomes from the male are added to the corresponding 23 from the female to produce 22 pairs and either a pair of X chromosomes or an X and a Y chromosome. The genes remain distinct, and a mechanism exists by which each allelomorph is replicated to be passed on to the cells of the body. In the process of reduction division, which occurs in the ovaries and testes, one member of each pair is passed on to each gamete. Thus, a homozygous parent can produce only one type of gamete as far as ability to produce a certain trait is concerned, while a heterozygous parent can transmit either of two types of gamete with respect to this specific trait. The fact which has just been stated was discovered by Gregor Mendel, and it is known as Mendel's first law or the *Law of Segregation*. This fact, plus the phenomenon of dominance, results in the appearance of certain traits in definite numerical frequencies. This will be illustrated next. This type of inheritance is known as Mendelian.

About one person in four cannot taste the organic compound, phenylthiourea, even though it is present in solution in a much larger amount than necessary for those to taste who do not have the defect. The substance is quite bitter to those who can taste it. The ability to taste the compound is transmitted by a pair of genes which can be designated TT, and they may exist in another form, represented by tt, responsible for inability to taste the substance. The two allelomorphs indicated, TT and tt, are both homozygous. The heterozygous allelomorph would be denoted by Tt. Thus, a given individual could have any of three possible genetic makeups, TT, Tt, or tt; but, he is either a taster or a non-taster of phenylthiourea. It is found that a person with either of the allelomorphs TT or Tt is a taster, while only one carrying the allelomorph designated tt is a non-taster. Therefore, T is said to be *dominant*, since its effect shows up if only one member of the allelomorphic pair is of this type. The only time that

the effect of the *recessive* member t can be evident is when it is present with another of the same type. Now, if two homozygous individuals, one of whom is a taster (TT) and the other a non-taster (tt), have children, all of the offspring will be tasters. This is true since all of the children will be heterozygous. One parent produces only genes carrying T , and the other produces only genes containing t ; hence only Tt allelomorphs appear in the zygotes. On the other hand, if the parents are both heterozygous, both will be tasters and the probability is that three out of four children born to them will be tasters while one will be a non-taster. The reason for this ratio is illustrated below.

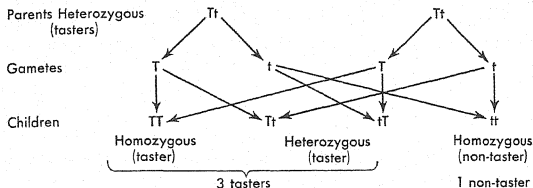


Figure 39-2. Ratio of types of children resulting from mating of parents who are heterozygous with regard to the gene which determines ability to taste phenylthiourea.

Using the same system, one may diagram the results if one parent is a homozygous taster (TT) and the other is heterozygous (Tt) or if one parent is a homozygous non-taster (tt) and the other is heterozygous (Tt). In the former case, the offspring all will be tasters, but half will be heterozygous and half homozygous. In the latter case, half will be heterozygous tasters and half will be non-tasters (tt). Finally, if both parents are non-tasters, each can transmit only t in the sperm or ovum and only the tt combination, or homozygous non-taster, can be produced.

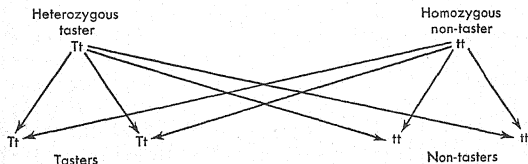


Figure 39-3. Results of mating of parent who is homozygous and can taste phenylthiourea with one who also can taste the compound but is heterozygous.

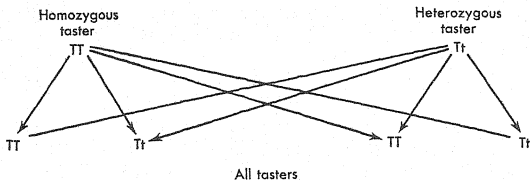


Figure 39-4. Predicted ratio of combinations resulting from mating of heterozygous taster and homozygous non-taster.

Mendel's second law, the *Law of Independent Assortment*, states: "When two or more genes segregate simultaneously, the distribution of any one of them is independent of the distribution of the others." In other words, if two characters segregate according to a 3:1 ratio, as when each parent is heterozygous with regard to each, each is randomly distributed. This means that there is no tendency for the parental combinations to be preserved in the offspring nor for dominant or recessive members of the pair of allelomorphs to segregate together. However, as explained below, Mendel's second law is subject to exceptions because of linkage.

Linkage and Crossing-Over

There are perhaps many thousands of allelomorphs and there are only twenty-three pairs of chromosomes, hence each chromosome carries a large number of genes. Since the chromosome is the vehicle for the gene, the latter cannot assort independently. Therefore, it is necessary to modify Mendel's second law to state that those genes which are carried in different chromosomes assort independently; while, in general, those which are carried in the same chromosome show a strong tendency to remain together. The term *linkage* refers to the latter situation. However, another phenomenon, known as *crossing-over*, occurs in chromosomes, which neutralizes in part the effects of linkage, and thus assures a greater variety of possibilities in the gametes. Cross over refers to interchange of sections of material between chromosomes. Genes are transferred from one homologous chromosome to the other; consequently, linked genes are not irrevocably joined, but can be combined in new ways.

Information on linkage in man is relatively meager except in the case of linked genes associated with sex. The relationship between sex and the X and Y chromosomes already has been explained (page 443). These chromosomes contain many genes in addition to those concerned with sex determination. These genes affect many characters which have no relation to sex except that they are carried in the same vehicle with the sex genes and hence tend to assort with them. Genes carried in the sex chromosomes are called *sex-linked genes*, and the characters concerned are *sex-linked characters*.

A notable example of a sex-linked character is *hemophilia* (see page 186 for characteristics). The gene which is concerned is recessive and is designated by *h*. A woman who is a carrier of the trait and is heterozygous (allelomorph represented by *Hh*) does not exhibit hemophilia. Half of the ova produced by her will carry *H* and the other half *h*. In a normal male, the X chromosome carries *H* and the trait is not represented in the Y chromosome, hence the male can pass on only *H* in the X chromosomes. The possible combinations and probable frequency of occurrence are diagrammed on page 448.

It is seen that four types of offspring are possible with regard to the character under consideration: (1) Normal females, (2) Carrier females, (3) Normal males, and (4) Hemophiliac males. There is an equal probability for each type, namely, a one to four chance. As in the example of Mendelian inheritance which is not sex linked, there is a 3:1 ratio of normals and hemophiliacs, but in this case the hemophilia appears in half of the sons and none of the daughters.

If a hemophiliac marries, the chances are that he will marry a female who has the allelomorph *HH*. In this case, none of the children would have hemophilia, but all of the daughters would be carriers (*Hh*). A marriage between a hemophiliac male and a carrier female (an occurrence which would be very improbable) theoretically could result in four types of children in equal numbers: normal sons, carrier daughters, hemophiliac sons, and hemophiliac daughters. However, since no females have been known to have full-fledged hemophilia (which is the form under consideration), it may be presumed that the last one of the four possible types listed cannot survive birth.

Color blindness is a benign condition which is inherited in the same manner as hemophilia. The possession of normal color vision has no prominent relation to survival. Color blindness occurs in females, but color-blind females are much less common than males. If a color-blind

male marries a normal female, none of the children will be color blind, since the Y chromosome is not concerned in the inheritance of the trait and the female can contribute only the normal character (C). If the

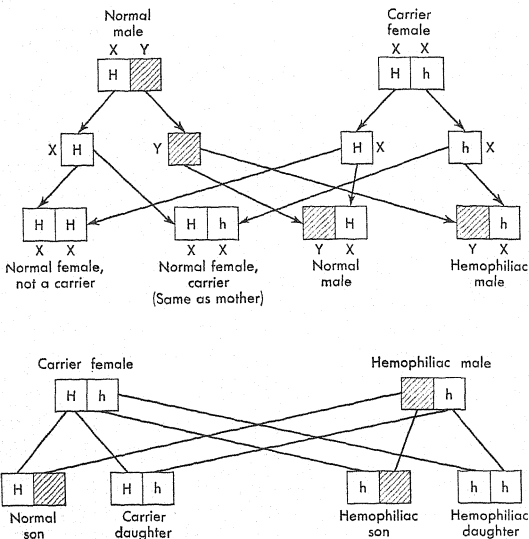


Figure 39-5. Inheritance of hemophilia.

Predicted ratio of combinations when parents are a normal male and a carrier female are shown in upper diagram and predicted ratio of combinations when parents are a hemophiliac male and a carrier female are shown in the lower diagram.

female is heterozygous (Cc) and the male is color blind, half of the male children and half of the female children would be predicted to be color blind. If father and mother are both color blind, all of the children would be color blind.

Mutation

From time to time, genes and chromosomes become changed and this may lead to a change in the characters influenced by them. According to E. B. Ford, mutation may be defined as *the inception of a heritable variation*. Precisely what causes these alterations in the molecules which provide the physical basis for inheritance is not clear, although experimentally such changes have been produced by several types of radiation. In any case, conditions exist in nature which predispose to mutation, hence mutations are said to occur "spontaneously."

Some biologists believe that mutations have been of great importance in evolution. The idea is held that if mutations are continually occurring and leading to inheritable alterations in the structure and function of organisms, some of these changes may be expected to be great enough to influence the chances of the individual for survival. If the change is such as to improve the individual's ability to survive under the conditions which exist in nature, then the relative number of individuals having this trait steadily would increase, while the relative number not having it would decrease and eventually might even disappear. In this manner, new traits having survival value continually would be incorporated, so that the species would become better and better adapted to its environment. Some mutations, on the other hand, lead to changes which not only do not have survival value, but may be so detrimental as to cause the death of the embryo.

Mutations are strictly localized phenomena. They may affect a specific gene and leave unchanged the genes on each side of it. Also, their frequency of occurrence is very low. It is estimated that one mutation in a million individuals is an approximate average mutation rate for a given gene, and a rate of one in 50,000 individuals is rarely exceeded. However, with increased exposure to radioactive materials produced by explosion of atomic bombs or to radiation in space (see Chapter 40), it is quite possible that the mutation rate will become increased.

Chapter 40

PHYSIOLOGICAL PROBLEMS IN SPACE TRAVEL

In 1951, Wernher von Braun, one of the leading rocket engineers, wrote: "I believe that the time has arrived for medical investigation of the problems of manned rocket flight, for it will not be the engineering problems but rather the limits of the human frame that will make the final decision as to whether manned space flight will eventually become a reality."

Borders of Space

What are some of the conditions and problems man would encounter in space travel? In one sense, the borders of space are those regions where the last traces of air become lost, or a distance from the earth of about 600 miles. The total pressure exerted by atmospheric air at sea level is about that amount which will support a column of mercury 760 mm. or 30 inches high. At an altitude of 18,000 feet, the atmospheric pressure is only about one half that at sea level, or 380 mm. of mercury. Thus, pressure decreases rapidly with altitude, but, since for each rise in altitude of 18,000 feet the decrease is one half of the remaining pressure, one must go to very high altitudes to get beyond the last traces of air. Such a boundary of space, the border between where there is only a trace of air and where there is no air at all, has no physiological significance, since human life can exist only at much lower levels where the atmospheric pressure is considerable. Hubertus Strughold, head of the Department of Space Medicine at the School of Aviation Medicine, San Antonio, Texas, states that space as a topographical concept is misleading when used in discussions relating to manned rocket flight. He emphasizes the fact that space in the physiological sense is reached when one goes

beyond the altitudes at which the air can fulfill the functions which are essential to life. When these functions are considered, it is seen that each becomes lost at a different altitude, but that all are lost at levels far below the upper reaches of the atmosphere. Let us consider first the border of space as far as the oxygen supply is concerned.

Oxygen Supply at Altitude

The relative proportions of the gases remain constant at all altitudes which support life, hence about one-fifth the atmospheric pressure at any altitude is due to oxygen. The fraction of the pressure due to oxygen at sea level is about 150 mm. of mercury. Therefore, with ascent to higher altitudes, the oxygen pressure goes down in direct proportion to the decrease in barometric pressure. A method has been developed whereby a subject can be exposed suddenly to a lowered pressure, such as would be encountered at a given altitude, and the time during which he retains consciousness at the simulated altitude can be determined. It is found that a subject who is decompressed abruptly to a pressure of the amount found at 26,000 feet loses consciousness within about 3 minutes. At the oxygen pressure found at 30,000 feet, a human subject can react to signals in an appropriate manner for a period of about 50 seconds, and at 46,000 feet he can react intelligently for only 11-15 seconds. This figure, the time during which useful consciousness is retained when one is exposed to a given oxygen tension, Strughold has called the time reserve. At levels from 46,000 feet up to 65,000 feet, the time reserve remains constant at 11-15 seconds. This is understandable, since this is just about how long it takes blood to flow from the lungs to the brain; hence if the oxygen supply were cut off completely at a given instant there would still be in the blood vessels a column of blood containing oxygen, and the end of this column would reach the brain in about 11-15 seconds. Thus, an altitude of around 46,000 to 52,000 feet represents a physiological boundary of space in that the amount of oxygen that can get into the blood at these levels is insufficient to maintain consciousness for any significant time and, if one is to travel beyond this level for any time at all, he must breathe oxygen at a higher pressure than the pressure of the surrounding air; therefore, some sort of enclosure is required.

Effects of Decompression

At 65,000 feet, another type of physiological problem is encountered, namely, lack of pressure as such. The higher the altitude, the lower the temperature required to cause water to boil. The temperature of the human body is around 98.6°F. Therefore, the water in the blood literally boils or vaporizes at or above this altitude. That this occurs has been demonstrated by explosively decompressing experimental animals to the barometric pressure which is found at 65,000 feet and observing that bubbles appear within the tissues and blood vessels. The circulation of the blood cannot be maintained under these conditions because the chambers of the heart become filled with bubbles. The bubbles in the heart interfere with entrance of blood from the veins and a further difficulty is that the cardiac muscular effort is used partly in compressing the vapor instead of moving the blood. If the animals are re-compressed within about one and one half minutes, they can survive the experiment although considerable damage to tissues is produced. Thus, one of the functions of pressure as such is to prevent the body fluids from vaporizing. It may be noted that boiling of body fluids occurs at altitudes well above those at which oxygen supply becomes a limiting factor in survival. If a space ship or space suit should develop a leak, and thus allow decompression at levels above 65,000 feet (12-13 miles), which is only a small fraction of the distance to the boundaries of the atmosphere, unconsciousness would supervene within a matter of seconds and would not be regained unless descent to well below 46,000 feet occurred within, at most, a minute or two. Hence, practically speaking, as far as the passenger in a space ship is concerned, space has been reached at 65,000 feet. From here on, either a sealed cabin or an air-tight suit containing gases under pressure is essential.

Effects of Motion

It would seem that the problems of ascent and descent in a rocket ship are as serious as those of survival in reasonable comfort once the ship has reached an orbit. Anyone who has felt his stomach "drop" when an elevator begins to ascend a little too fast, is aware of the fact that acceleration has rather striking effects on the body. During and since World

War II, much work has been done to determine the effects of motion on human subjects. These forces exerted on the body as a result of motion are expressed in comparison with the pull of gravity, hence the results are in G units. One G is the pull which is exerted on the body at rest on the surface of the earth. To go back to the elevator analogy, if a person weighing 150 pounds stands on a scale with the elevator at rest, the scale will read 150 pounds. If the elevator starts to ascend, the reading on the scale will be something above 150 depending upon how fast the elevator is gaining speed. If it moves up so that its velocity is 32 feet greater at the end of each second of ascent, the weight recorded on the scale will be 300 pounds, or two G, and so on. The body can withstand only a limited amount of increased pull produced in this manner. In the actual studies of the effects of increased G on the human body, as a matter of convenience, centrifugation usually is employed. Everyone knows that it is possible to swing a bucket of water in a circle in the vertical plane at a speed such that the water will not fall out even though at one point in the circle the bucket is upside down. This illustrates that a force is being developed as a result of the circular motion, and this force is more than enough to counteract the effect of gravity even at relatively slow speeds. Centrifugal force is increased, at a given circle radius, as the speed is increased, hence any desired G can be developed in a centrifuge. In the centrifugation of human subjects who are in the sitting position, it is found that unconsciousness very quickly develops at around five times the pull of gravity, and a pull of greater than three G should not be applied for prolonged periods during which the subject is performing tasks. The major difficulty which is encountered when the body is subjected to increased G, for example, in direct ascent, is that the blood, being fluid, tends to be left behind in the lower parts while the body is moved on. In the elevator analogy, or in a person being centrifuged in the sitting position with his head toward the center of the circle, the blood will tend to remain in or be thrown into the blood vessels of the legs and the lower part of the body, and hence the amount of blood returning to the heart to be pumped will decrease. At five to six G, in the sitting subject, the return of blood to the heart is reduced so severely that the output of the heart is insufficient to maintain an adequate blood flow to the brain, hence unconsciousness develops.

Now, in the acceleration diagram of a three stage rocket ship shown by von Braun, the maximum acceleration produced by the first booster is nine G. This is much more than that which quickly produces unconscious-

ness unless the subject remains in a horizontal position with reference to the earth as the rocket rises vertically. The second booster of a rocket ship is estimated to produce a maximum acceleration of eight G, and the third stage develops a maximum of three G. Therefore, it would be necessary to throttle down the rocket in the terminal stage of each of the first two stages of power application if the crew is to be able to perform tasks during the ascent. However, it is probable that an automatic pilot would be used to control the rocket during stages one and two.

According to Heinz Haber, acceleration sufficient to subject the body to three G would need to be sustained for 9 minutes and 31 seconds in order to produce a velocity which would carry a space ship to an orbit.

Temperature Regulation in a Space Ship

Another problem on ascent is temperature regulation. Human life can exist within only a relatively narrow temperature range, and man is reasonably comfortable within a still more restricted range. The temperature problem is introduced in space flight mainly because movement of an object through the air at a rapid rate causes heating. Even in a fast-flying aircraft, cabin temperature may increase to 70°F. above that of the surrounding air. It is well known that small meteors which enter the earth's atmosphere at high speeds become heated to incandescence.

In addition to the problems of heating from flight through air at high speeds, there are wide variations in temperature of the air at different altitudes. Temperature decreases with altitude up to about 6 miles where it is around -55°F. In the stratosphere, which is the shell of atmosphere from 6 to 20 miles, the temperature is approximately constant. Then temperature shows a rise to about +170° at around 40 miles and decreases to -28° at 60 miles. The practical point is that considerable extremes of temperature would be encountered in flight through the earth's atmosphere, hence insulation of the capsule containing the crew would be essential, and perhaps temperature-regulating equipment would be needed during the ship's rapid ascent or descent through the air.

Once an object reaches an altitude beyond the earth's atmosphere, it is heated by the sun's rays almost exclusively. A certain amount of radiant heat reaches the object per square foot of surface exposed to the sun's rays. If all of this were absorbed by the object, enough heat would be taken up per hour to raise the temperature of 440 pounds, or about 55

gallons, of water 1°F. However, the amount of radiant heat which is absorbed by an object varies from almost 100 per cent, if the object has a dull black surface, to almost zero if it has a polished silver surface. Therefore, the surface of a space ship could be designed to absorb any per cent of the radiant heat that is calculated to be needed to maintain the temperature at the desired level. In making the calculations, it would be necessary to take into consideration the fact that the human body itself continually liberates heat, and the conservation of this heat might be very important if the sun's rays were cut off by the earth.

Effects of Weightlessness

In plans for space flight, it is visualized that rockets carrying crews and materials will be sent out from the earth to reach an orbit at a distance well beyond the earth's atmosphere, say 1000 miles from the earth's surface. Here the rocket, with the power cut off, would circle as a satellite. Centrifugal force, related to its speed, would be exactly balanced against the pull of gravity. It is thought that rockets could carry crew and materials so that a space station or platform could be constructed at which a space ship could be assembled to be sent off to the moon or other points. In view of such plans by the engineers, it is pertinent to consider the physiological problems of survival in a rocket ship "coasting" in space and also problems of exit from and return to the ship.

Once the ship is coasting, it and the objects within it, including the passengers, are in a sense weightless. The ship and contents are falling freely through space. Under these circumstances, a person sitting in a chair would feel no pressure against his body, since the chair also is falling freely, and he would have no sensory mechanism for telling him his position with respect to the earth. He could sit in a chair placed either on the ceiling of the cabin or on the floor and would detect no difference. In trying to walk, he would have great difficulty, since there would be nothing to keep his feet from sliding. On the other hand, to move from one side of the cabin to the other or from floor to ceiling would be quite easy. This would be done simply by giving a quick push against the wall. Only a slight muscular effort would be required to send the body across to the opposite side. One could, in a space suit, step outside the ship and remain there at a constant distance from it. The cargo could be dumped out and would follow along with the ship. If a passenger should

jump out of the ship the muscular effort would push him and the ship a certain distance apart. More important, although he would be only a short distance away from the ship, he would have no way of getting back. He could be retrieved if he were tossed a rope or extended a "hand" in some manner to pull him back, but he could not help himself. To work on assembling a space platform, the workman would require his own individual rocket motor to move him about and get him back to the ship. Or, on the other hand, everything could be kept connected with ropes along which the workmen could move. At the same time, the workman would be carrying a tank of oxygen, or have it pumped to him through a hose from the ship.

Just what psychological effects would result from a prolonged feeling of weightlessness is not known. However, it does not seem that the sensation of weightlessness would be intolerable; and, in fact, it is possible that one would adapt to the sensation quite readily. Orientation with regard to surrounding objects, in this case, would depend entirely upon sight.

Control of Environment in a Sealed Cabin

The regulation of the environmental conditions within a space ship, including provision of oxygen and removal of carbon dioxide, water vapor, and odors for prolonged periods poses no special problems beyond those which have been encountered in submarine navigation; however, in a space ship it would be necessary to keep weight as low as possible. Small animals have been kept within a small air-tight container for as long as 30 days with oxygen being added as needed and carbon dioxide and other vapors being removed. This was done with growing animals and no alteration of the growth curve was produced by the experiment.

The gondola of the balloon which went to 72,345 feet was sealed for $5\frac{3}{4}$ hours. Oxygen was supplied from a mixture of 45 per cent liquid oxygen and 55 per cent liquid nitrogen. A fan continuously forced the gondola air through an apparatus for absorbing water and carbon dioxide. Pressure was maintained at the level found at 13,000 feet. The gondola was rotated by means of an external fan which worked well despite the rarefied atmosphere. One portion of the surface of the gondola was black and the other white, so that any proportion of black to white surface area could be exposed to the sun. Thus, a comfortable temperature was achieved. One and seven-tenths pounds of liquid oxygen was used

by the two men during the time that the gondola was sealed. This is at the rate of about 3.4 pounds of liquid oxygen per man per day.

Effects of Radiations

A very real medical problem at high altitudes is the loss of the shielding effect of the atmosphere with regard to several types of radiations. From about 100 miles out, objects encounter radiations of cosmic and solar origin in their original form and intensity.

Most of the ultraviolet rays are filtered by the atmosphere before they reach sea level, yet exposure of the skin for a relatively short time will produce the well-known reactions. Actually, ultraviolet rays are absorbed by ozone, a molecule consisting of three atoms of oxygen. Above the ozone, one would be exposed to the full intensity of the ultraviolet rays and sunburn would occur in a much shorter time than at sea level. However, the hull of any ship which protects the crew sufficiently from other hazards already considered would readily block out these rays. Windows of the ship could be made of glass which screens out most of the ultraviolet.

The major problem with regard to radiation hazards is protection against cosmic rays. In their space or "primary" form, these consist of up to 79 per cent of protons (or hydrogen nuclei) and 20 per cent of alpha particles (or helium nuclei). The remaining one per cent is composed of nuclei of heavier atoms. The latter so-called "heavy primaries" have a tremendously high penetrating power. When they enter the atmosphere, they collide with nuclei of the atoms of the gases which compose the air, and as a result, lose their original powerful form. The ionization and collision products—namely, protons, electrons, neutrons, mesons, and gamma rays—permeate the atmosphere. The latter types of radiation, known as secondary rays, have less energy than the primary rays. Thus, at sea level we are not exposed to primary rays, while above 120,000 feet one would be exposed to the primary cosmic radiations perhaps to the same degree as in interplanetary space.

Cosmic radiations actually are particles moving at high speeds and hence may be thought of as bullets of infinitesimal size. They penetrate the human body and produce alterations in the atoms within the cells. Thus, they can produce illness and, in greater amounts, death. One can be shot with a certain number of these bullets and the body can repair

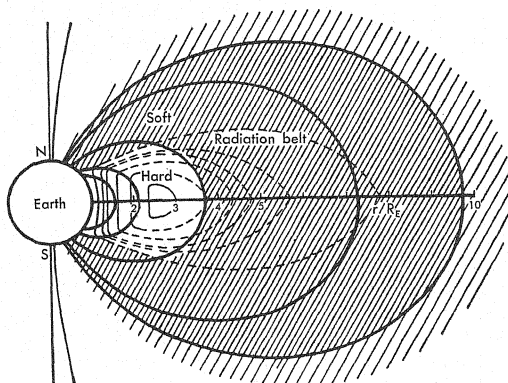


Figure 40-1. Distribution of radiation belts around the earth. The lines emanating from the Earth indicate the lines of force of the Earth's magnetic field. The closed lines give contours of equal radiation intensity for the hard radiation belt, which is of cosmic ray origin. Its maximum is in the vicinity of 1.5 Earth radii where the radiation exposure is about 10 r per hour. Its intensity begins to increase at about 600 km (according to the theory) and may reach out as far as 10 Earth radii (40,000 miles) at the equator. Note that the regions around the poles are clear. The soft (auroral) radiation belt is indicated by cross-hatching and overlaps somewhat with the hard radiation belt at higher latitudes and greater altitudes.

(Reproduced by permission from S. F. Singer, "Effects of Interplanetary Dust and Radiation Environment on Space Vehicles," in *Lectures in Aerospace Medicine* conducted at the School of Aviation Medicine, Brooks Air Force Base, Texas, 1960.

the damage. As the number of penetrations per unit of time is increased, a level is reached at which repair cannot keep pace with the damage. Protection against the particles is by shielding. Much research has been done to determine (1) the amounts of these rays at various altitudes, (2) the maximum dose of radiation that can be tolerated, and (3) the least shielding that is required to keep the exposure below the maximum which can be tolerated. However, the answers are far from complete. One reason for this is that the damage to the body may become manifest only after a delay of months, years, or even after generations if the genetic effects are taken into consideration. The types of damage seen include production of cataracts, leukemia, genetic changes, and sterility.

Chapter 41

PHYSIOLOGY IN DISEASE

Disease is characterized by either interruption or alteration of the functions of a part or organ of the body. The derangement of function leads to the signs and symptoms of the specific disease. In some diseases the physiological alterations are preceded by gross or microscopic anatomical changes, or lesions, while in other instances no specific structural abnormalities can be demonstrated. In the latter case the lesion can be said to be biochemical rather than anatomical.

The distinction between *signs* and *symptoms* is in general that the former are changes that are known by physicians to be associated with deranged functions of organs but which may not give rise to a complaint on the part of the patient. Conversely, symptoms are those changes which are a source of annoyance or discomfort to the patient and which have led him to consult a physician. When a doctor performs a complete physical examination and obtains an extensive history of the patient's complaints, he may accumulate a list of signs and symptoms which by itself may provide the basis for diagnosis of a specific disease. However, certain laboratory tests which include analyses of the blood and urine, routinely are performed, if these tests have not been done lately; and in some instances the diagnosis cannot be made until additional specific laboratory tests, suggested by the signs and symptoms, are performed.

Genetic Versus Environmental Bases for Disease

An abnormality, as explained in Chapter 39, can be on a genetic basis. Those diseases or abnormalities which are inherited "run in families" according to a pattern that would be predicted on the basis of well known principles of genetics. Other diseases clearly are produced either by the

presence of or lack of something in the environment. One of the best examples of the former is infection, and an example of the latter is deficiency of intake of one or more of the vitamins.

It might appear at first consideration that it would be easy to classify a given disease as being on an hereditary or an environmental basis, however, actually it may be difficult since what is inherited in some cases is susceptibility to a disease rather than inheritance of the disease itself. This seems to be true, for example, of tuberculosis. Before tuberculosis was brought under control to the extent that it is at present most persons in urban areas became infected with the bacillus which produces tuberculosis. Most persons overcame the infection, while others succumbed. The difference in effectiveness of the reactions of the body to the organism probably were, in part, on a genetic basis.

Some diseases are congenital but not genetically caused. The abnormalities in this case are acquired in utero. Infections in the mother may be transmitted to the fetus and produce alterations, or any dietary deficiency in the mother may be reflected in changes in the fetus.

Nutritional Deficiencies

One large category of diseases includes those caused by lack of intake of vitamins, minerals, essential amino acids, essential fatty acids, etc. Examples of a number of these have been referred to in other chapters. Starvation itself causes changes similar to those seen in pituitary cachexia, as studied in some of the concentration camps during World War II.

Diseases due to dietary deficiencies are not common in the United States but are prevalent in certain areas of Asia and Africa. For example, beriberi (page 366) is one of the world's most common diseases but is rarely seen in this country except among chronic alcoholics who substitute alcohol for food.

Injury and Death by Physical Agents

The production of abnormalities, disease, and death by physical agents rapidly is becoming of increasing importance, due largely to the automobile. Accidents ranked fourth among the causes of death in 1959 and accounted for about 1 in 20 deaths during that year. Death from accidents

ranked first for the age group 2-24 in 1959. Motor vehicles accounted for two-fifths of the total number of accidental deaths at school ages.

Mechanically induced damage results in bruises, abrasions, cuts, fractures, hemorrhage, etc. The reactions to hemorrhage and the production of shock in such instances have been described. Also, the basis for circulatory changes following head injuries was explained in the discussion of effects of rapid increase in intracranial pressure. The main danger from extensive burns is the tendency for shock to develop.

In Chapter 40 the effects on the body of certain types of radiation were described.

Diseases Caused by Chemicals

Some corrosive chemicals, such as strong acids, produce changes in the skin similar to those resulting from heat, and the reparative changes which result are similar to those which occur following burns.

There are innumerable substances which are poisonous to the body when breathed or ingested. These act in many different ways. They may have some subtle action such as the neutralizing of activity of enzymes or they may simply lead to shock from excessive loss of body fluids as a consequence of vomiting and diarrhea.

Carbon monoxide is a dangerous poisonous gas. Bases for its effects are discussed on page 305. Some of the heavy metals, such as lead, are dangerous since the effects may be insidious and the diagnosis may not be apparent at first. In the past, children sometimes developed lead poisoning from chewing on toys painted with paint containing lead. At present usually lead paint is not used on toys.

The problem of addiction to drugs comes under this heading. With the great increase in the number of drugs available there are many more drugs which lead to addiction. Pharmacologists distinguish between *habituation* and *addiction*. The former may be exemplified by the taking of a sleeping tablet every night and a cup of coffee every morning. Either could be discontinued at any time with no striking reaction or ill effects. In the case of addiction, on the other hand, the body makes certain adjustments to the drug so that less effect is produced by a given dose, and the addict builds up the intake to a level which is far beyond that needed to produce strong reactions in the normal subject. The phenomenon of development of tolerance is characteristic of reactions to addictive drugs;

and just as characteristic is the appearance of withdrawal symptoms when the subject suddenly is taken off of the drug. The best known addictive drugs are morphine (the active principle in opium) and cocaine.

Infection and Defenses Against It

One of the triumphs of modern medicine is the bringing under control of the diseases caused by microorganisms. This has resulted in the great prolongation of life expectancy as compared with what it was in 1850. The three leading causes of death at present are of the degenerative type (affecting the cardiovascular system) and cancer. These and accidents accounted for 71.6 per cent of deaths in 1959 in the United States. In the years from 1900-1910 tuberculosis appears as either first or second in the list of causes of death; today it does not appear in the first 10. Formerly, the United States experienced epidemics of yellow fever, typhoid, cholera, diphtheria, and smallpox, but these diseases all have been brought under control. As an example, in the United States the death rate from diphtheria was 40.3 per 100,000 at the beginning of this century, and by 1940 the rate had decreased to 1.1 per 100,000. This has been accomplished mainly by use of immunization.

Mortality for the Ten Leading Causes of Death

United States, 1959

RANK	CAUSE OF DEATH	NUMBER OF DEATHS	DEATH RATE PER 100,000	PER CENT OF TOTAL
	<i>All causes</i>	1,656,814	939.1	100.0
1	Diseases of the heart	641,044	363.4	38.7
2	Malignant neoplasms	260,047	147.4	15.7
3	Vascular lesions affecting central nervous system	191,376	108.5	11.6
4	Accidents	92,080	52.2	5.6
5	Certain diseases of early infancy	67,934	38.5	4.1
6	Influenza and pneumonia	55,039	31.2	3.3
7	General arteriosclerosis	34,622	19.6	2.1
8	Diabetes mellitus	28,080	15.9	1.7
9	Congenital malformations	21,780	12.3	1.3
10	Cirrhosis of the liver	19,242	10.9	1.2

Source: National Office of Vital Statistics, U. S. Public Health Service. *Vital Statistics of the United States*. Washington, D. C.: Superintendent of Documents, Government Printing Office, 1959. (Vol. 7, No. 13, July 22, 1959.)

The diseases produced by either microorganisms or viruses include (in addition to those mentioned above) meningitis, pneumonia, gonorrhea, syphilis, malaria, dysentery, and many others. Each organism is adapted to attacking the human body at a certain site and has its own weapons. The body likewise has at its disposal certain defenses against the invading microorganism.

The reaction of the body to infection by staphylococcus is quite characteristic. This is the organism which is famous for causing the production of pus, as in boils. When the staphylococcus is implanted in a tissue, e.g. in the skin, and has begun to multiply and liberate toxic substances polymorphonuclear neutrophil cells are attracted to the site of infection and ingest the bacteria. In some way the need for increased production of neutrophils is signalled to the bone marrow and the proportion of these cells is increased. The infected site becomes literally walled off by neutrophil cells if the infection persists. At the same time the blood supply to the region is increased, as indicated by warmth and reddening of the skin, and fibroblasts are stimulated to help wall off the infected area. Many of the white blood cells are destroyed and on liquefaction enter into the production of pus. At this stage the lesion is known as an abscess. This may break through the skin and drain, or if deeper it may be necessary to open it by surgery. When the organisms have been killed a series of reparative processes is initiated which results eventually in a scar.

If the body does not succeed in walling off the invading microorganisms and they enter the circulatory system to be disseminated throughout the body, the condition is known as septicemia. When this has occurred usually the physician must depend upon the chemotherapeutic agents or antibiotic compounds to bring the infection under control.

In contrast to the immediate and relatively violent reaction to the staphylococcus the response to the bacillus which causes tuberculosis is slow and mild. Effects may become evident only after weeks or months, or an individual who is resistant may overcome the infection without ever being aware of having been exposed. In the latter case a scar may be detected in the lung by fluoroscopic examination years after the infection occurred.

It is a generally known fact that once a person has recovered from any of several infectious diseases he will not contract the disease again. Having the disease has resulted in the development of *immunity*. This is related to the fact that substances produced by infecting organisms

liberated in the body act as antigens which induce the development of antibodies which are capable of neutralizing the ill effects of the organism or re-infection (see page 187). This provides the basis for immunization. The bacterial or viral antigens may be introduced into the skin of a person who has not had the disease and induce the production of antibodies. The immunity which is built up in this way is known as *active*. On the other hand, blood may be taken from a person who has had the disease, and hence has developed antibodies, and be given to another person who has not had the disease. This is called *passive* immunity, since it does not involve any reaction in the cells of the person receiving the injection. Active immunization is made use of to protect against contracting diseases such as smallpox and diphtheria. Passive immunization is of greatest value if the person already has been exposed to the disease or has contracted it.

The substances other than antibodies that are used to treat infectious diseases are included in two main groups: chemotherapeutic agents and antibiotics. The chemotherapeutic agents are substances not produced by living organisms which for one reason or another are poisonous to microorganisms in concentrations which can be tolerated by the human body. The sulfonamide compounds are included in this category. The antibiotics are substances produced by living organisms, usually fungi, which have the effect of interfering with the growth of microorganisms. Penicillin (produced by a fungus of the genus *Penicillium*) was the first of a large series of substances of this type to be obtained for therapy of infectious diseases.

A wide variety of chemotherapeutic and antibiotic compounds is useful since some of these are quite effective against some bacteria while less effective or ineffective against others. Also, it is useful to have several compounds which attack the same microorganism, since some strains may have become resistant to the specific compound while still being sensitive to the action of another. It is obvious from the foregoing that the most effective treatment can be instituted when the physician knows which organism is responsible for the disease and which agents are most effective against the organism. Hence an effort is made to identify the organism as early as possible, although in specific acute infections time is so important that treatment may be instituted before laboratory reports are received and if necessary may be modified later on the basis of the reports.

Psychosomatic Problems and Stress

What goes on in the mind has an effect on the body; psyche affects soma, hence the term *psychosomatic*. There are a number of diseases which appear to be aggravated by or even caused by psychic factors. An example is the businessman who develops a peptic ulcer which does not bother him and begins to heal while he is on vacation and recurs when he goes back to work.

There are numerous ways by means of which severe prolonged stress can predispose to the development of disease or to the progression of abnormalities which already are present. For many years some physicians have felt that nervous strain promotes progression of coronary atherosclerosis, leading to heart attacks. Gradually evidence has been accumulating that this condition tends to progress more rapidly in persons having a relatively high blood cholesterol level. This fits with the fact that cholesterol is one of the substances which is utilized in the formation of the atherosclerotic plaques in the arteries. Now it is shown that severe nervous strain may be associated with a marked rise in the blood cholesterol level.

In very severe stress the sympathetic nervous system and adrenal glands (both medulla and cortex) are activated and produce characteristic changes (page 403). If the stress is prolonged signs of exhaustion of the adrenal cortex may develop and administration of adrenal cortical hormones may be an important part of the treatment.

Students of psychosomatic medicine are interested in the idea that different types of strong emotions may give rise to characteristic somatic responses. Resentment or worry, for example, may lead to different changes than those associated with fear or anger. The belief that resentment and worry tend to lead to development of peptic ulcer, whereas fear and anger do not, has been supported by the results of studies of changes in gastric motility and secretion, and of the blood supply to the gastric mucosa.

Tumors

Abnormal growths in the body are referred to as tumors or neoplasms (new growths). Tumors are classified initially as benign or malignant.

The benign type tends to remain localized and commonly is enclosed in a capsule. The malignant type of tumor is characterized by its tendency to invade the surrounding tissues from its original site and also to become disseminated to other parts of the body via either the lymphatic channels or the blood vessels. The latter phenomenon is known as *metastasis*. If a malignant tumor is detected early before metastasis has occurred it can be excised completely, and hence a cure can be achieved.

Tumors may develop from any type of tissue. Strictly speaking, *cancer* or *carcinoma* is a malignant tumor developing from epithelial tissue. A malignant tumor developing from connective tissue or muscle is a *sarcoma*. Obviously, there are many different types of tumors; and each type has certain characteristics, but also there are great variations in the manifestations of each type.

The great problem in cancer research, of course, is to discover why cells which should be more or less quiescent suddenly begin to divide and grow. Thus far it has been demonstrated that a number of chemicals have a cancer-producing effect when applied to epithelium in experimental animals. They are referred to as carcinogens. Some of these are encountered in the environment and hence conceivably could be implicated in the production of cancer in man.

Carcinogens have been found in the tars produced by burning of cigarettes; and this fact, along with the demonstration of a correlation between the amount of smoking and the incidence of cancer of the lung in smokers has led to the general acceptance of the view among physicians that cigarette smoking is an important cause of lung cancer. Also, statisticians have accumulated evidence of a greater incidence of cancer of the lung among non-smoking city dwellers than among non-smoking country dwellers, so that the breathing of fumes prevalent in cities (presumably exhaust from automobiles) must be considered as another factor which might be responsible for the increased incidence of lung cancer.

It seems well demonstrated that excessive exposure of the skin to X-rays will cause cancer of the skin. A number of dentists who used X-rays early after their discovery, and did not take precautions to avoid repeated exposure of their hands, developed cancer of the skin of the hands. Now precautions are taken and this does not occur. Also, cancer of the skin is more common in persons who are exposed excessively to the sun's rays. It is to be expected that in the future a number of specific causes of cancer will be discovered and preventive measures accordingly will be indicated.

Aging and Degenerative Changes

The degenerative changes include, roughly, the alterations in tissues which tend to occur in some degree in all persons as a part of aging. For example, loss of elasticity of tissues is characteristic. This involves the arteries, the crystallin lens, the lungs, etc. The associated conditions respectively are arteriosclerosis, presbyopia, and emphysema. The age at which such changes occur is variable, and also the degree of the change is variable. Such conditions can be referred to as disease logically only when they are more severe than the normal for the respective age group.

Other conditions which do not regularly accompany aging but which usually develop only in persons beyond say 45 to 50 and which are characterized by being more or less slowly progressive sometimes are designated as degenerative diseases. This group would include atherosclerosis as distinguished from arteriosclerosis. The latter refers to the loss of elasticity or "hardening of the arteries" and occurs in some degree in every elderly person; whereas atherosclerosis, the deposition of plaques of fatty material which tends to become calcified and to encroach steadily upon the lumen of the artery, occurs in a large per cent of but not in all elderly persons. Furthermore, atherosclerosis sometimes develops in young persons.

The incidence of degenerative diseases has increased largely as a consequence of the fact that a larger number of persons now reach the ages at which these conditions occur. The frequency of occurrence of degenerative diseases within a given age group in most instances is not much different than it was a number of years ago.

Heart disease is by far the leading cause of death in the United States, and most of these deaths are the consequence of atherosclerosis in the coronary arteries leading to a cutting off of the blood supply to a portion of the ventricular musculature. The changes in the heart muscle under these conditions are designated as myocardial infarction.

Lesions of the blood vessels in the central nervous system rank third among the leading causes of death. The most common cause in this case is rupture of a brittle artery in the brain resulting in stroke (apoplexy).

Degenerative changes and diseases affecting the joints (rheumatism and arthritis) are very common in persons beyond middle age. These conditions do not rank high among causes of death, but are responsible for discomfort and disability in a large number of persons.

The causes of the degenerative changes in tissue with aging are obscure. It may be expected, however, that research on aging will reveal at least some of the factors which are responsible; and, if so, to decelerate the changes might become possible. At present the relatively early aging of some persons and much later aging of others seems to be largely on a genetic basis with environment, under most circumstances, playing a minor role.

Etiology Unknown

In a considerable number of diseases the causative factors are unknown. This includes some very common diseases, such as essential hypertension (page 263) and some of the rheumatic diseases. Rheumatoid arthritis apparently is a specific disease and it is quite distinct from the degenerative type of arthritis, or osteoarthritis, which tends to occur in some degree in all elderly persons. It usually starts in early adult life. No infective cause has been demonstrated although sometimes fever is present. For the most part the joints of the limbs are affected, especially of the wrist and hand and of the ankle and toes, while the vertebral column, hip joints, and shoulder joints usually are not affected. Initially the synovial membrane of the joint cavity is inflamed and involvement spreads to adjacent tissues. The disease tends to wax and wane for years until it burns out, leaving some degree of deformity.

There are several diseases of the central nervous system which are characterized mainly by the destruction of the myelin sheaths. Multiple sclerosis is an example. Although a number of theories have been advanced it must be admitted that the etiology of multiple sclerosis is unknown.

A large number of less common diseases, including several which affect the skin, are of unknown etiology. In most of these diseases it appears that genetic, nutritional, and infective bases have been ruled out. Hence, it appears that the researcher must look for injury of some sort, or altered reactivity of body tissues, or even more obscure causes in an attempt to determine the causes of these diseases.

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WEIGHTS AND MEASURES

LINEAR

1 meter	= 100 centimeters	= 39.37 inches
1 millimeter	= 0.1 centimeter	= 0.001 meter
1 centimeter	= 0.01 meter	= 0.39 inch
2.54 centimeters	= 1.0 inch	
1 micron	= 0.001 millimeter	= 0.000,001 meter
1 kilometer	= 1000 meters	= 0.6214 miles
1.605 kilometers	= 1.0 mile	

WEIGHT

1 kilogram	= 1000 grams	= 2.2 pounds
1 gram	= 15 grains	
454 grams	= 1 pound	
30 grams	= 1 ounce	
4 grams	= 1 dram	
1 milligram	= 0.001 gram	= 1/60 grain
1 microgram	= 0.001 milligram	= 0.000,001 gram

VOLUME

1 liter	= 1000 milliliters	= 1.057 quarts
3.785 liters	= 1 gallon	
1 milliliter (synonymous with cubic centimeter)		= 0.001 liter
4 milliliters		= 1 fluid dram
15 milliliters	= ½ fluidounce	= 1 tablespoon
30 milliliters		= 1 fluidounce
1000 milliliters		= 1 liter

PREFIXES

a, ab	- away from, away
a, an	- without, e.g., anhydrous, anoxia
ante	- before in time or place
anti	- against
bi	- twice or double
bio	- from the Greek, <i>bios</i> , life
circum	- around
contra	- against, opposed
di	- twice
dia	- through, e.g., dialysis
dys	- bad or difficult, e.g., dyspnea, dysphagia, dyspepsia
ecto	- situated on, without or on the outside
endo	- within
eu	- good, well. Similar to <i>bene</i> (beneficial), e.g., euphoria, eupnea
entero	- pertaining to the intestine
ex	- out, away from
gastro	- pertaining to the stomach
hem, haem	- pertaining to the blood
hemi	- one half
hetero	- dissimilarity or unlikeness, e.g., heterogeneous
homeo	- similarity, same as homo-, e.g., homeostasis
hyper	- above, beyond, or excessive, e.g., hyperactive, hypertension
hypo	- below, under, or deficient, e.g., hypoactive
infra	- beneath or under
inter	- between or among, e.g., intercellular
intra	- within or inside, e.g., intracellular—within the cell
ipse, ipsi	- same, e.g., ipsilateral, on the same side
macro	- large, e.g., macroscopic
mega- megal-	- large or great, e.g., megacolon
meso	- middle or between
meta	- (1) change or transformation, e.g., metamorphosis - (2) after or next
micro	- small, e.g., microorganism, microcosm

multi	- many or much, e.g., multicellular
myo	- some relation to muscle
necro	- dead, e.g., necrosis (death of tissue), necropsy (autopsy)
noci	- injurious, e.g., nociceptive (receiving injury)
olig, oligo	- few or little, e.g., oligemia (deficient blood volume)
ortho	- straight or normal, e.g., orthopedics
osteo	- referring to bone
poly	- many
pre	- before or in front of
pro	- before, in front of, in behalf of
post	- after or behind
retro	- backward
semi	- half
sub	- under, near, or almost
super	- above or excess, same as <i>supra</i>
syn	- union or together, e.g., synchronous, synthesis, synapse
ultra	- excess or beyond
uni	- one, unicellular
vas	- vessel or dish. Vaso—referring to vessel
vivi	- alive, e.g., viviparous (to give birth to live young) vivisection (to dissect living animals)

GLOSSARY

Abdomen. Region of the body containing the viscera other than heart and lungs (i.e., intestine, liver, kidneys, etc.); in mammals, but not in other vertebrates, bounded anteriorly by diaphragm.

Abducens Nerve. Sixth cranial nerve. Supplies external rectus eye-muscle.

Acapnia. Decreased amount of carbon dioxide in the blood.

Accessory Nerve. Eleventh cranial nerve. Really a branch of the vagus, clearly separate only in mammals.

Accommodation. Adjusting the focus of the eye. In man and a few other mammals, occurs by changing curvature of lens; at rest, lens is focused for near objects by contraction of ciliary muscles (controlled by parasympathetic) in ciliary body which narrows diameter of the ring formed by ciliary body and allows lens to round off a little by its own elasticity.

Acetabulum. Cup-like hollow on each side of hip girdle in which head of femur (thigh bone) fits, forming hip joint.

Acetone. A ketone (q.v.) found in considerable quantities in the blood and urine of diabetic patients.

Acetylcholine. Substance secreted at the ends of many nerve fibers (cholinergic fibers), when nerve impulses arrive there. Where a nerve fiber ends at a synapse, acetylcholine may be the agent which stimulates the contiguous nerve cell and hence in effect mediates the impulse, and similarly where the fiber connects with an effector. After secretion, acetylcholine is rapidly destroyed by the enzyme cholinesterase. It is the acetyl ester of choline (q.v.).

Acid. A compound which dissociates in aqueous solution to yield hydrogen ions.

Acidosis. A condition in which the amount of bicarbonate in the blood is below normal.

Acoustic. Concerned with hearing. *A. nerve*, Auditory nerve (q.v.).

Acquired Characteristics, Inheritance of. Transmission to offspring of variations which appeared in the parents as responses to environment. The view that such inheritance occurs is commonly known as Lamarckism or Neo-Lamarckism. Such inheritance is thought not to be of importance in organisms reproducing sexually. The gametes are not affected by acquired variations in such a way as to transmit them to the offspring.

ACTH (Corticotropin). Adrenocorticotrophic hormone, secreted by anterior lobe of pituitary, controlling secretory activity of adrenal cortex. A protein or polypeptide.

Action Potential. A localized change of electrical potential across the membrane of a nerve or muscle fiber which marks the position of an impulse as it travels along the fiber. In the absence of an impulse, the inside is electrically negative and the outside is positive (the resting potential), and during the passage of an impulse past any point on the fiber, the inside becomes positive and the outside negative. This wave of potential change is an easily detectable and measurable aspect of a nerve impulse.

Active Transport. Transfer of substance accomplished by means of expenditure of energy from metabolism. Substance may be moved to region of higher concentration.

Actomyosin. A complex of two proteins, actin and myosin, forming a major constituent of muscle.

Adaptation. (1) Evolutionary. Any characteristic of living organisms which, in the environment they inhabit, improves their chances of survival and ultimately of leaving descendants, in comparison with the chances of similar organisms without the characteristic, i.e., adaptations are the characteristics established in a population by natural selection. An adaptation to a particular feature of the environment means a characteristic which is an adaptation because it reduces destruction by that particular feature. An adaptation to a particular *activity* of an organism means simply a characteristic which makes possible or improves performance of that activity without necessarily being measured in terms of survival, though usually that is implied. (2) Of receptors. Change in excitability of a sense organ as a result of continuous stimulation such that a more intense stimulus becomes necessary to produce the same activity, e.g., contact of an object with the skin at once excites the touch receptors, but if contact is maintained the touch receptors quickly cease to respond because the stimulus required to excite them has increased. Different receptors differ much in the rate of adaptation.

Adenosine Triphosphate. ATP (q.v.).

Adipose Tissue. Fatty tissue. Connective tissue, the cells of which contain large globules of fat.

Adrenal Gland. An organ of hormone secretion. There is a single pair, one near each kidney, in man and other mammals. Each gland has two components distinct in function, but closely fused together. (a) Medulla, the inner part of the gland, embryologically derived from nervous tissue (probably neural crest), secreting epinephrine. (b) Cortex, the outer part of the gland, embryologically derived from the lining of the coelom, secreting at least three types of hormones chemically related to sex hormones (steroids).

Adrenaline. See *Epinephrine*.

Adrenergic. Of a motor nerve fiber, secreting at its endings either nor-epinephrine or epinephrine when nerve impulse arrives there. These substances stimulate the effector innervated by the nerve fiber. Many sympathetic motor nerve fibers are adrenergic. Cf. *Cholinergic*.

Adrenomimetic. Having an action on visceral effectors similar to that of epinephrine.

Aerobic Respiration. Respiration in presence of free (i.e., gaseous or dissolved) oxygen. Cf. *Anaerobic Respiration*.

Afferent. Leading toward, e.g., of nerve fibers conducting impulses towards central nervous system (sensory fibers).

After-Discharge. Persistence of reflex response after cessation of stimulation of sensory nerve or receptor.

Agglutination. Sticking together, e.g., of red blood corpuscles.

Agnosia. Loss of power to recognize the import of sensory stimuli.

Albinism. Lack of skin pigments. In man, commonly due to a single recessive gene.

Albumen. One of the types of protein found in blood plasma. Has lower molecular weight than globulins.

Alimentary Canal. The gut; a tube concerned with digestion and absorption of food.

Alkali. A substance which in aqueous solution dissociates to yield OH ions.

Alkaloids. Group of nitrogen-containing, basic organic compounds present in a few families of plants; possibly end products of nitrogen metabolism. Of great importance because of their poisonous and medicinal properties, e.g., atropine, cocaine, morphine, nicotine, quinine, strychnine.

Alkalosis. Condition in which there is an increased amount of bicarbonate in the blood.

Allantois. Sac-like outgrowth of ventral side of hinder part of gut present in embryos of amniote vertebrates; represents a large and precocious development of urinary bladder. Allantois grows during development so that it extends outside the embryo proper, to lie in wall of yolk sac of birds and reptiles, or under chorion of mammals. It is always covered with connective tissue containing a rich network of blood vessels, communicating with embryonic circulation. In mammals, the allantoic blood vessels supply blood to placenta serving not only for respiration, but for nutrition and excretion; cavity may be large and accumulate urine, but is often very small; most of allantois and its blood vessels are detached from embryo at birth.

Allelomorphs (Alleles). Two or more genes are said to be allelomorphs (of each other) or allelomorphic (to each other) when they (1) occupy the same relative position (locus) on homologous chromosomes, and, when in the same cell, undergo pairing during meiosis (q.v.); (2) produce different effects on the same developmental processes; and (3) can mutate one to another. See *Heterozygous*, *Homozygous*.

Allergy. Unusual or exaggerated susceptibility to a substance which is harmless in similar amounts to most people.

All-or-None Law. Certain irritable tissues in standardized conditions have only two possible reactions to stimuli of whatever intensity: either no response, or response of one invariable strength.

Alveolus. (1) Minute air-filled sac in lung, thin walled and surrounded by blood vessels. There are large numbers of alveoli in each lung, and it is

through their surfaces that the respiratory exchange of oxygen and carbon dioxide occurs. They connect with the mouth by a system of ramifying air tubes (bronchi and bronchioles). (2) Expanded sac of secretory cells which forms internal termination of each duct in many glands (e.g., mammary glands). (3) Cavity in jaw bone into which a tooth fits.

Amino Acid. An organic acid having an NH_2 group usually on the carbon atom adjacent to the COOH group.

Amino Group. NH_2 group.

Amnion. The embryo of amniote vertebrates (reptiles, birds, mammals) develops in a fluid-filled sac. The wall of this sac has two layers of epithelium with mesoderm and coelomic space between, formed usually by folds of yolk-sac ectoderm and mesoderm which grow up around, and eventually roof over, the embryo. The inner epithelium of the wall is the amnion, though the term is also applied to the whole sac. The outer epithelium is usually called the chorion. Amniotic fluid within the sac provides a fluid environment for the embryo, necessary for animals reproducing on land. In mammals, the fluid probably cushions embryo against distortion by maternal organs pressing on it.

Amniote. Any reptile, bird, or mammal. The *Amniota* form a grouping of vertebrate classes contrasted with the *Anamniota*. Consists of the essentially land-living vertebrate classes whose embryos have an amnion and allantois (Reptilia, Aves, Mammalia).

Ampere. Unit of intensity of electric current, being the current produced by one volt acting through a resistance of one ohm.

Amylase. Enzyme which causes hydrolytic cleavage of the starch molecule.

Anabolism. Process by which simple substances are converted by living cells into more complex substances.

Anaerobic Respiration. Occurring in the absence of oxygen.

Analogous. (1) An organ of one species is said to be analogous to an organ of another when both organs have the same function and when they are not homologous (q.v.). Possession of analogous organs does not imply a close evolutionary relationship of the organisms bearing them. It merely indicates adaptation to similar conditions. (2) May also be used simply for similarity of function, whether or not the organs in question are homologous.

Anaphase. Stage of cells division when daughter chromosomes are separating toward poles of spindle.

Androgen. General name for any substance with male sex-hormone activity, i.e., responsible for development and maintenance of many male sexual characteristics. Natural androgens in vertebrates are steroids, produced mainly by testis. See *Testosterone*, *Estrogen*.

Androgenic. Producing masculine characteristics.

Anemia. Deficiency in the amount of hemoglobin in the blood.

Anion. An ion carrying a negative charge, so named because it is attracted toward the anode.

Anode. Positive pole of a battery.

Anorexia. Lack of appetite.

Anosmia. Lack of sense of smell.

Anoxia. Subnormal oxygen tension in blood or tissues, i.e., oxygen lack. Also called hypoxia.

Anterior. Toward the front; in man, synonymous with ventral.

Anterior Root. Of nerve, synonymous with ventral root (q.v.).

Antibiotic. Substance produced by living organism which diffuses into its surroundings and is toxic there to individuals belonging to other species; e.g., penicillin, produced by *Penicillium notatum*, antagonizes many species of bacteria.

Antibody. A specific substance produced in the body in response to an antigen.

Anticholinesterase. A substance which blocks the action of enzymes which promote the hydrolysis of acetylcholine, e.g., eserine.

Anticoagulant. Substance which prevents the clotting of blood, e.g., heparin.

Antidiuretic Hormone (ADH). Hormone secreted by posterior lobe of pituitary. Stimulates water reabsorption by urinary tubule, hence diminishes volume of urine. Deficiency causes diabetes insipidus.

Antigen. Any foreign substance which incites the formation of antibody when introduced into the blood or tissues.

Anus. The opening of the alimentary canal to the exterior through which food residues are expelled.

Aorta. In man and other mammals, the artery which leaves the heart (from the left ventricle), and through which passes the oxygenated blood supply for the entire body to be distributed via the systemic circuit.

Aorta, Dorsal. Artery of vertebrates through which passes oxygenated blood to all the body except the head and in some species the front limbs. Lies just below vertebral column throughout most of the latter's length.

Aorta, Ventral. Large artery of fish and *embryonic* amniotes, which leads from ventricle of heart, and gives off branches to gills or aortic arches.

Aortic Arches. Paired arteries (usually six) of vertebrate embryos, connecting ventral aorta with dorsal aorta by running up between gill slits or gill pouches on each side, one in each visceral arch. In fish, develop into arteries carrying blood to and from gills. In tetrapods, the two most anterior pairs disappear, the third pair forms proximal part of carotid arteries, fourth becomes systemic arch, fifth disappears, and sixth forms part of pulmonary arteries.

Aphasia. Loss of power of expression by speech.

Apneusis. Cessation of breathing with the chest in the inspiratory position.

Appendage. Any considerable projection from the body of an animal. *Paired a.* One of a bilaterally symmetrical pair of appendages. Two such pairs occur in all gnathostome vertebrates. This gives rise to the name tetrapod.

Apraxia. Loss of ability to perform purposeful movements.

Aqueous Humor. Fluid which fills space between cornea and vitreous humor of the vertebrate eye. The iris and lens lie in it.

Artefact. Something which does not occur in the undisturbed living tissue or organism, but was produced in it during investigation, or during its preparation for investigation.

Arteriole. Terminal vessels of arterial tree, less than $\frac{1}{2}$ mm. diameter. Smooth

muscle of wall well developed, and under control of autonomic nervous system. Acts as a kind of stopcock regulating blood flow through capillaries.

Artery. Blood vessel carrying blood from the heart towards the tissues.

Ascorbic Acid (Vitamin C). Vitamin required by man and other primates. Water soluble. Deficiency causes scurvy, and prevents collagen formation (e.g., in healing wounds).

Assimilation. Absorption and building up of simple foodstuffs, or products of digestion of foodstuffs, into complex constituents of the organism.

Astereognosis. Loss of power to recognize objects by feeling them.

Ataxia. Lack of strength, generalized muscular weakness.

Ataxia. Lack of muscular coordination, clumsiness.

Atlas. First vertebra modified for joint with skull. It consists of a simple bony ring, and there is a peg (odontoid process) on the next vertebra (axis) which projects forward into the ring (through which spinal cord also runs). This peg represents part of the atlas (its centrum) which has become detached and fused to the axis. Nodding the head takes place at skull-atlas joint; rotating head at atlas-axis joint.

Atom. The smallest quantity of an element that can exist and retain the chemical properties of the element.

ATP (Adenosine Triphosphate). A co-enzyme of many reactions. One of the phosphate groupings of ATP is readily transferred to other substances by enzyme action, taking with it a considerable amount of energy. The transfer of phosphate from ATP seems to be the main mechanism by which organisms make energy available for chemical synthesis, muscular contraction, osmotic work, etc. ATP is re-formed from adenosine diphosphate as a result of catabolic processes, the energy of which is thus made available for various kinds of work through ATP. See *Phosphagen*.

Atrium. Synonym of Auricle (q.v.).

Atrophy. Diminution in size of an organ, or in amount of a tissue or constituent of a tissue.

Auditory Capsule. Part of skull enclosing auditory organ.

Auditory Nerve (Acoustic Nerve). Eighth cranial nerve of vertebrates, innervating inner ear.

Auditory Organ. Sense organ for detecting sound. In vertebrates, the auditory organ (see *Ear, Inner*) also detects position in relation to gravity and acceleration.

Auricle (Atrium). One of the chambers of the heart; receives blood from veins and passes it to ventricle. In land-living vertebrates, which breathe mainly or entirely by lungs, there are two auricles, one receiving oxygenated blood from lungs, the other deoxygenated from rest of body.

Auto-Assay. Assay of a substance by its effect on some tissue or process within the same organism that produces the substance.

Autonomic Nervous System. Motor nerve supply to smooth muscle (e.g., in gut, blood vessels, etc.), heart, and glands. Consists of sympathetic system and parasympathetic system.

Auxin. See *Hormone*.

Axis Cylinder. Axon (q.v.).

Axon. The long process of a nerve cell, normally conducting impulses away from the nerve cell body. Cf. *Dendrite*. Often covered by myelin. See *Nerve Fiber*.

Backbone. See *Vertebral column*.

Baroreceptor. See *Pressoreceptor*.

Base. Same as alkali.

Basophilic. Staining strongly with basic dye. Especially characteristic of nucleoproteins, and hence of nucleus (during mitosis of which, basophily is localized in chromosomes).

Bel. Unit of sound intensity in terms of perception of sound.

Bilaterally Symmetrical. Capable of being halved in one, and only one, plane in such a way that the two halves are approximately mirror images of each other. Usually, this plane lies anteroposteriorly and dorsoventrally, thus separating similar right and left halves.

Bile. Secretion of liver passed through bile duct to duodenum. Important in digestion of fats, which, through action of bile salts, are broken into minute droplets (emulsified). Contains also pigments which are waste products of hemoglobin destruction.

Bile Duct. Duct from liver to duodenum of vertebrates. Conveys bile. See *Gall Bladder*.

Bile Salts. Sodium salts of taurocholic and glycocholic acids (bile acids, see *Steroids*) secreted in bile. Strongly lower surface tension, emulsifying fat.

Binocular Vision. Type of vision in which eyeballs can be so directed that image of the same object falls on a special place in both retinas. See *Fovea*.

Binomial Nomenclature. The present method of naming species of animals and plants scientifically. The name is in two parts (binomial), one part designating the species and the other part designating the genus (q.v.) to which it belongs, and, therefore, applied to other closely related species, if any, but to no other genus. The name of the genus is written first with a capital letter, and the name of the species is written last, usually with a small letter, e.g., *Homo sapiens*.

Bio-Assay. Quantitative estimation of biologically active substances by the amount of their actions on some process in a standardized condition in living organisms.

Biochemistry. Study of chemical processes occurring in living things.

Biophysics. Study of physical processes in living things.

Bladder. See *Gall Bladder*, *Urinary Bladder*.

Blastula. Stage of embryonic development of animals, at or near the end of period of cleavage, and immediately preceding gastrulation. Usually consists of a hollow ball of cells.

Blood. The fluid normally present in the heart and blood vessels.

Blood Clotting (Blood Coagulation). Conversion of liquid blood to clot. A soluble blood protein (fibrinogen) is converted into insoluble threads (fibrin) by an enzyme (thrombin). Thrombin is formed from a blood protein (pro-

thrombin) by an activator (thrombokinase) liberated from injured tissues or from blood platelets.

Blood Corpuscle. Cell which circulates in blood. See *Red Blood Cell*, *White Blood Cell*.

Blood Group. Blood of similar groups may be mixed without clumping of blood corpuscles. There are four main groups, A, B, AB, and O. Agglutination occurs when blood from any two different groups is mixed, owing to a reaction between substances (agglutinogens) in corpuscles and other substances (agglutinins) in plasma.

Blood Plasma. The fluid portion of the blood. See *Blood Serum*, *Plasma Proteins*.

Blood Platelets. Minute bodies, probably fragments of cells, in mammalian blood. Roughly 250,000 per milliliter of human blood. Also called thrombocytes. For function, see *Blood Clotting*.

Blood Pressure. Usually refers to pressure of blood in main arteries, which in normal subjects fluctuates roughly between 120 and 80 mm. of mercury according to stage of heart beat (maximum at systole, minimum at diastole). Pressure throughout the whole circulation diminishes from arteries next to heart round to veins next to heart; in mammals, reaching atmospheric or less in large veins.

Blood Serum. Fluid expressed from clotted blood or from clotted blood plasma. Roughly, plasma deprived of clotting constituents.

Blood Sugar. Glucose circulating in blood. Supplied to blood by liver (where it is stored as glycogen) and removed therefrom by all body cells for use as food. Maintained at a fairly constant level (80–150 mg. per 100 ml. blood), chiefly controlled by hormones (insulin, epinephrine, and hormone from anterior pituitary). If level is too low (hypoglycemia), there are serious symptoms; if too high (hyperglycemia as in diabetes mellitus), glucose is excreted by kidney.

Blood Vessel. Tube through which blood flows. See *Artery*, *Arteriole*, *Capillary*, *Venule*, *Vein*.

Body Cavity. Internal cavity of most triploblastic animals in which many organs are suspended. Bounded externally by body wall.

Bone. Skeletal substance peculiar to vertebrates. Consists of cells distributed in a matrix consisting largely of collagen fibers together with a complex salt (bone salt) mainly of calcium and phosphate. Bone salt is responsible for hardness; collagen for tensile strength.

Bowman's Capsule. Part of renal corpuscle. Small sac ($\frac{1}{2}$ to $\frac{1}{10}$ mm. diameter in man); inward projection of its wall contains tuft of capillaries (glomerulus); from it leads uriniferous tubule.

Brachial. Of the arm. *B. plexus.* Interconnections formed in shoulder region between the spinal nerves supplying the forelimb (arm) of tetrapods (fifth to ninth spinal nerves in man).

Brain. Anterior part of central nervous system, present in almost all bilaterally symmetrical animals, enlarged in connection with aggregation of sense organs in head region.

Brain Stem. Vertebrate brain excluding cerebral hemispheres and cerebellum.

Bronchiole. Small air-conducting tube of lung, arising as branch of a bronchus, terminating in alveoli. Smooth muscle abundant in walls, controlling size of lumen.

Bronchus. Large air tube of lung. Each lung has one large bronchus, connecting it to trachea; within the lung the bronchus branches into smaller and smaller bronchi, and finally into bronchioles.

Buffered. Resisting changes in pH when acid or alkali is added. A property of many biological fluids.

Buffer Nerve. Same as depressor nerve; afferent nerves innervating the pressoreceptors of the carotid sinuses and aortic arch. They are in the IXth and Xth cranial nerves.

Buffer Substance. A substance in a fluid which lessens the change in hydrogen ion concentration which otherwise would be produced by adding acids or alkalis.

Caecum. A blindly-ending branch of gut or other hollow organ.

Calorie. Unit of heat. A small calorie is the amount of heat required to raise the temperature of one gram of water one degree centigrade. A large Calorie, or kilogram calorie, is 1000 small calories. The capital C is used in writing the latter.

Calorimetry. Measurement of amount of heat absorbed or given off.

Canine Tooth. "Dog" or "eye" tooth. Usually conical and pointed, one on each side of upper and lower jaws, between incisors and premolars.

Capillary, Blood. Minute tube (very roughly 5-20 microns internal diameter) conveying blood which it receives from an arteriole and gives up to a venule, with a wall consisting of a single layer of flattened cells (endothelium), supported by some fine connective tissue fibers. Capillaries in very large numbers permeate almost all the tissues. The main exchange of substances between blood and tissues occurs through capillary walls.

Capsule. Connective tissue covering an organ, providing mechanical support.

Carbohydrate. A group of chemical compounds which includes sugars, starches, dextrin, glycogen, and cellulose. They are so named because hydrogen and oxygen atoms are present usually in the same ratio as in water, i.e., 2:1.

Carbon Cycle. World-wide circulation of carbon atoms brought about mainly by living things. Essentially, carbon from carbon dioxide is built into complex organic compounds by plants during photosynthesis. These compounds are then broken down again to carbon dioxide during respiration and after death by decay of the plants; or the plants are eaten by herbivorous animals which in turn may be eaten by carnivores and the carbon compounds are sooner or later broken down to carbon dioxide by respiration or death and decay of the animals.

Carboxyl Group. The COOH radical which is characteristic of organic acids.

Carcinogen. Producer of cancer, e.g., certain hydrocarbons which produce cancer when injected into, or painted repeatedly on, susceptible animals.

Cardiac. Concerning the heart. *C. cycle*, succession of muscular contractions

and movements of heart valves which make up activity of heart from one beat to next. *C. end of stomach*, region of stomach joined by esophagus. *C. muscle*, special kind of muscle, arranged in a syncytial meshwork of muscle fibers with cross striations, which gives motive power to heart. Undergoes automatic rhythmic contractions.

Carnivora. Order of placental mammals containing flesh-eating forms (cat, dog, lion).

Carnivore. Flesh eater. In narrower sense, member of order Carnivora.

Carotene. Orange pigment (hydrocarbon $C_{40}H_{56}$) occurring in chloroplasts, and in plastids in other plant parts where chlorophyll is absent, e.g., carrot roots.

Carotene of food is changed into vitamin A in vertebrate liver.

Carotid Artery. Main artery supplying blood from heart to head of vertebrates.

One on each side. See *Aortic Arches*.

Carpal Bones. Bones of the proximal part of the foot of the forelimb (roughly of the wrist) in quadrupeds. Eight bones in man. Articulate on proximal side with radius and ulna, on distal side with metacarpals.

Carpus. Region of foreleg of quadrupeds containing carpal bones; roughly the wrist.

Cartilage. Skeletal tissue of vertebrates consisting of rounded cells scattered in a resilient carbohydrate-containing matrix, with numerous collagen fibers.

Cartilage Bone. A bone which replaced embryonic cartilage, e.g., any limb bone, pelvic girdle, vertebral column, parts of skull such as auditory capsule.

Catabolism. The phase of metabolism in which substances are broken down into simpler materials; the opposite of anabolism.

Cathode. Negative pole of a battery.

Cation. An ion which is positively charged and hence is attracted toward the negative pole of a battery.

Caudad. In a caudal direction, toward the tail.

Cell. Discrete mass of protoplasm, bounded by a plasma membrane. The structural unit of living organisms.

Cell Body (Perikaryon). The mass of cytoplasm with contained nucleus, from which arise the branches of a nerve cell.

Cell Division. Division of cell into two. The nucleus usually divides by mitosis, occasionally by amitosis. The cytoplasm divides by constriction into two in animals.

Cell Membrane. See *Plasma Membrane*.

Cell Theory. Theory that all animals and plants are made up of cells and their products, and that growth and reproduction are fundamentally due to division of cells.

Cement. Bone-like substance which makes a thin covering to root of vertebrate tooth (i.e., below gum level) and in some mammals (e.g., ungulates) covers parts of enamel of crown.

Center, Nerve. Region of central nervous system with a restricted special function, e.g., respiratory center in medulla of vertebrates which controls respiratory movements. The term is physiological rather than anatomical. Cf. *Nucleus*

- Central Nervous System (CNS).** The brain and spinal cord.
- Centriole.** Minute granule, present in many resting cells, just outside the nuclear membrane. Doubles before mitosis, and at mitosis the two centrioles move apart and form the poles of the spindle, and the centers of the asters when present.
- Centrum.** Massive part of each vertebra, lying ventral to spinal cord. Replaces embryonic notochord. Each is firmly but flexibly attached to adjacent centra by collagen fibers.
- Cephalad.** Toward the head.
- Cephalic.** Pertaining to the head.
- Cerebellum.** Outgrowth of anterior end of dorsal surface of hindbrain. A conspicuous part of the brain in birds and mammals (with a cortex of gray matter in mammals).
- Cerebral Hemispheres.** Paired outpushings of front end of forebrain of vertebrates. In mammals, hemispheres are largest part of brain with a much folded cortex.
- Cerebrospinal.** Of the brain and spinal cord.
- Cerebrospinal Fluid (CSF).** Fluid which fills the cavity inside brain and spinal cord, and the pia-arachnoid space outside them, the inside and outside communicating by holes in the roof of the hindbrain.
- Cerumen.** Ear wax. Secretion of skin glands of external ear passage in mammals.
- Cervical.** Of the neck.
- Cervix (Cervix Uteri).** Cylindrical posterior part of the uterus of mammals, which leads into the vagina.
- Chemoreceptor.** Receptor adapted for responding to chemical changes, particularly the receptors in the carotid and aortic bodies which respond to changes in oxygen tension, carbon dioxide tension, and pH of the blood.
- Chemotaxis.** Taxis in which stimulus has the form of a gradient of chemical concentration, e.g., movement of polymorph leucocytes towards bacteria.
- Cholesterol.** A sterol found in all animals studied, but not in plants.
- Choline.** An organic base, probably a vitamin for some mammals which do not synthesize all they require. Choline is a constituent of certain important fats (lecithin) and of acetylcholine.
- Cholinergic.** Term applied to the nerve fibers which liberate acetylcholine when a nerve impulse passes. Cf. *Adrenergic*.
- Cholinesterase.** An enzyme which hydrolyzes acetylcholine. An esterase is any enzyme which inactivates an ester, the latter being a substance formed from an acid and an alcohol by the removal of water.
- Cholinomimetic.** Having an action similar to that of acetylcholine.
- Chondriosomes.** See *Mitochondria*.
- Chordata.** Phylum of animals with notochord, hollow dorsal nerve cord, and gill slits. Includes subphyla Vertebrata (Craniata) and Protochordata.
- Chorion.** Embryonic membrane of amniote vertebrate, consisting of outer ectodermal epithelium with layer of mesoderm beneath. See *Amnion*. In mammals, the superficial layer enclosing all the embryonic structures; its outer epithelium is trophoblast; forms placenta.

Choroid. Layer, in vertebrate eye, immediately outside retina, containing blood vessels and pigment.

Choroid Plexus (Choroid Plexus). Numerous projections into cavity (ventricle) of brain of the non-nervous epithelium which constitutes its roof in some regions, enclosing tufts of blood vessels. Secretes cerebrospinal fluid. One plexus occurs in roof of each of the four ventricles in man.

Chromaffin. Having an affinity for chrome salts; in general the chromaffin tissue includes the epinephrine-producing cells in the adrenal medulla and in and around a number of ganglia of the sympathetic system.

Chromatid. One of the two strands which result from duplication of a chromosome during prophase and metaphase of mitosis or meiosis, before they separate. After they separate they are known as daughter chromosomes.

Chromatin. The more stainable portion of the cell nucleus.

Chromosome. One of the small dark-staining bodies which are seen in the nucleus of a cell at the time of cell division.

Ciliary Body. Thickened rim of choroid of vertebrate eye, at border of cornea, containing *ciliary muscles* which are concerned in accommodation.

Ciliated Epithelium. Sheet of cells with cilia on exposed surface. The cilia beat in coordinated rhythm. Found in respiratory passages.

Cilium (Pl. Cilia). Fine cytoplasmic thread projecting, along with many others, from the surface of a cell. Cilia of a cell, or of a whole epithelium, lash with orderly beat in a constant direction.

Classification. Organisms are classified in a hierarchical series of groups. The smallest group regularly used is the species (q.v.). Species which are more like each other than like other species are grouped together in a genus; similarly, genera are grouped into families, families into orders, orders into classes, and classes into phyla or divisions. All groups of any one kind, e.g., all families are supposed to have approximately the same 'weight,' e.g., every family is supposed to differ from its related families belonging to the same order by a roughly equal amount and the same degree of difference should be found in every order.

Clavicle. Bone of ventral side of shoulder girdles of many vertebrates. Collar-bone of man.

Cleavage. Repeated subdivision of the zygote cytoplasm, accompanying a corresponding nuclear mitosis, which follows fertilization. In animals, often produces a mass of small cells, the blastula.

Clitoris. Homologue of penis in female mammal.

Cobalamine (Vitamin B₁₂). Cobalt-containing vitamin required by many organisms. Needed for normal production of red blood cells.

Coccyx. Tail vertebrae fused together. In man, consists of three to five vestigial vertebrae.

Cochlea. That part of the inner ear concerned in the reception of sound with analysis of its pitch. A projection of the saccule. It is coiled like a snail shell.

Coelom. Main body cavity of many triploblastic animals, in which gut is suspended. Situated in the mesoderm, lined by epithelium.

- Coenzyme.** Organic compound playing essential part in reaction catalyzed by some enzyme, usually acting as temporary carrier or intermediate product of the process.
- Collagen.** Fibrous protein which, on boiling, yields gelatin. One of principal skeletal substances, binding cells and tissues together in vertebrates. Fibers made of collagen have a high tensile strength (exemplified by tendon). Leather is tanned, i.e., fixed, collagen of dermis. See *Fibroblast*.
- Colloid.** A state of matter in which particles are dispersed in a medium. The dispersed particles are larger than ordinary crystalloid molecules, but not large enough to settle under the influence of gravity.
- Colon.** Large intestine excluding the narrower terminal rectum.
- Commissure.** Bundle of nerve fibers connecting right and left sides of brain or spinal cord.
- Compensatory Hypertrophy.** Increase in size of residual part of a tissue or organ, some of which has been removed or put out of action, e.g., when one kidney is removed, the other enlarges. See *Hypertrophy*.
- Competitive Inhibition.** Where two processes compete for some raw material (substrate) which both use; inhibition of one process by diversion of available supplies of the raw material to the other. Particularly used of competing enzyme systems.
- Compound.** A substance which consists of two or more chemical elements in union.
- Conditioned Reflex.** A reflex based on experience. The original sensory component (i.e., the stimulus, sense organ, and sensory nerve path involved in it) is replaced by a different sensory component, while the motor component (i.e., the response) remains unchanged.
- Conduction.** Passage of physiological disturbance through a cell or tissue as a result of stimulation at one point, e.g., conduction of nerve impulse.
- Cone.** Kind of light-sensitive nerve cell present in the retina. Concerned in color discrimination and in the most acute discrimination of detail. See *Fovea*, *Rod*.
- Conjunctiva.** The layer of mucus-secreting epidermis, with underlying connective tissues, covering the white of the eye and lining the eyelids.
- Connective Tissue.** Vertebrate tissue consisting of *connective tissue fibers* usually mainly of collagen, but with varying amounts of elastin and reticulin; scattered cells (fibroblasts and macrophages); blood and lymph vessels; tissue fluid in spaces; and in amorphous matrix. Supporting function. Many modifications occur.
- Coracoid.** Bone of shoulder girdle of vertebrates, on ventral side. Meets scapula at glenoid cavity. Reduced to small process of scapula in man.
- Cord.** See *Spinal Cord*, *Umbilical Cord*.
- Corium.** See *Dermis*.
- Cornea.** The transparent epidermis and connective tissue at front surface of the eye of vertebrates, overlying iris and lens. Mainly responsible in land vertebrates for the refraction which results in focusing an image on retina.
- Cornification.** Conversion of cells into keratin, e.g., in epidermis.

Coronary Vessels. Arteries and veins of vertebrates carrying blood to and from heart muscle.

Corpus. The body, the main part of an organ.

Corpus Luteum. Temporary organ of internal secretion of the hormone progesterone. Formed in mammals in interior of a ruptured Graafian follicle after ovulation by ingrowth of follicle wall which becomes yellow secretory *luteal tissue* (corpus luteum means "yellow body"). Formation occurs as a result of action of luteinizing hormone (q.v.) of pituitary. If ovulation does not result in fertilization, corpus luteum persists and continues secreting during part or all of pregnancy.

Cortex. The outer layers of an organ as distinguished from its inner substance.

Corticotropin. See *ACTH*.

Cortisone. One of the hormones produced by the cortex of the adrenal gland. 17-hydroxy-11-dehydrocorticosterone.

Cranial Nerve. Nerve emerging from brain of vertebrate, i.e., originating within the skull as distinct from spinal nerve which emerges from spinal cord. Dorsal and ventral roots (see *Nerve Root*) of several segments exist among these nerves, but (unlike those of spinal cord) remain separate. Each is numbered and named as a separate nerve. There are 12 pairs in mammals. See *Olfactory, Optic, Oculomotor, Trochlear, Trigeminal, Abducens, Facial, Auditory, Glossopharyngeal, Vagus, Accessory, Hypoglossal* nerves. (These are listed in order I-XII).

Craniata. See *Vertebrata*.

Cranium. Skull of vertebrates.

Crenation. Notched appearance of the borders of the erythrocytes produced by shriveling.

Cutis. Skin; composed of epidermis and dermis.

Cyanosis. Bluish appearance of the skin caused by insufficient oxygenation of the blood in the cutaneous vessels.

Cytochrome. Mixture of similar substances (proteins, with an iron-containing prosthetic group allied to that of hemoglobin) concerned in cell respiration, widely distributed in aerobic organisms. Its oxidation by molecular oxygen, and subsequent reduction by oxidizable substance in the cell (both processes under influence of enzymes) is main way in which atmospheric oxygen enters into metabolism of cell.

Cytology. Study of cells.

Cytolysis. Dissolution of cells, particularly by destruction of the surface membranes.

Cytoplasm. The protoplasm of the cell exclusive of that found in the nucleus. Protoplasm in the nucleus is called nucleoplasm.

Darwinism. Theory of evolution by natural selection.

Daughter Cells (Daughter Nuclei). The two cells (or nuclei) resulting from division of a single cell.

Deamination. Removal of amino (NH_2) group. In mammals, occurs to many amino-acid molecules by action of enzymes in liver and kidney.

Decibel. One-tenth of a bel, the latter being the unit of sound intensity used in studying audition.

Decidua. Mucous membrane (endometrium) lining uterus in the thickened and modified form it acquires during pregnancy in many mammals. Some or all of the decidua comes away with the placenta at birth. See *Placenta*.

Deciduous Teeth. Milk teeth. First of the two sets of teeth which most mammals have; similar to the second (permanent) set which replaces it except in having grinding teeth corresponding only to the premolars, not to the molars, of that set.

Deficiency Disease. Disease due to deficiency of some essential food substance, e.g., vitamin, mineral element, or essential amino acid.

Deglutition. Swallowing.

Dehydrogenase. Enzyme which catalyzes oxidation of substrate by removing hydrogen from it. Cf. *Oxidase*.

Dendrites. Branching cytoplasmic projections of a nerve cell which have synapses with, and receive impulses from, axons of other nerve cells.

Dental Formula. Formula indicating the number of each kind of teeth. The number in the upper jaw of one side is written above that in the lower jaw of one side, and the categories are given in the order: incisors, canines, premolars, molars. The human formula is I 2/2, C 1/1, P 2/2, M 3/3.

Dentine. Main constituent of teeth. Like bone in structure, but contains no cells, though cell processes penetrate it from cells in pulp cavity of tooth.

Depressor Nerve. An afferent nerve which has the function of promoting a fall in blood pressure; the nerves from the pressoreceptors of the carotid sinuses and aortic arch.

Dermis (Corium). Innermost of the two layers of the skin of vertebrates, the outer being the epidermis. Much thicker than epidermis. Consists of connective tissue with abundant collagen fibers mainly parallel to surface, scattered cells, blood and lymph vessels, sensory nerves. Sweat glands and hair follicles project down from epidermis into dermis.

Dextrin. Polysaccharide carbohydrate formed as an intermediate product in hydrolysis of starch.

Dextrose. See *Glucose*.

Dialysis. Method of separating small molecules, e.g., salts, from colloids, e.g., proteins, in mixed solution, by putting mixture in bag made of a membrane, e.g., collodion, permeable to small but not to large molecules, with excess water outside the bag into which small molecules diffuse.

Diaphragm. Sheet of tissue, part muscle, part tendon, covered by serous membrane, separating cavities of thorax (occupied by lungs and heart) from cavity of abdomen (occupied by intestine, liver, etc.). Present only in mammals.

Diaphysis. Shaft of a long limb bone, or central portion of a vertebra, in mammals. See *Epiphysis*.

Diastase. See *Amylase*.

Diastole. The phase of the cardiac cycle during which the heart muscle is not

- in a state of contraction, hence the phase during which no blood is being pumped out of the heart.
- Digestion.** Breakdown of complex foodstuffs by enzymes to simpler compounds which can be absorbed.
- Digit.** Finger or toe of pentadactyl limb. Contains phalanges.
- Dioptr.** The unit of measurement of refractive power of a lens; it is the reciprocal of the focal length of the lens in meters.
- Diploid.** Of a nucleus, having the chromosomes in pairs, the members of which are homologous so that twice the haploid number is present. Characteristic of almost all animal cells except the gametes.
- Disaccharide.** Any one of a class of sugars which yield two monosaccharides on hydrolysis; sucrose, lactose, and maltose are examples.
- Distal.** Farthest from the center or median line; opposed to proximal.
- Distance Receptor.** Exteroceptor responding to external stimuli (e.g., light, sound) which allows orientation of the animal to source of the stimuli.
- Diuresis.** Increased rate of secretion of urine.
- Dizygotic Twins (Fraternal Twins).** Twins developed as result of simultaneous fertilization of two separate ova. Such twins are genetically no more alike than brothers and sisters. Cf. *Monozygotic Twins*.
- DNA. (Deoxyribonucleic acid).** See *Nucleic Acid*.
- Dominant.** A gene which produces the same character when it is present singly along with a specified allelomorph (heterozygous), as it does when double in number (homozygous), is said to be dominant to that allelomorph. The allelomorph (q.v.) which is ineffective in the heterozygote is said to be *recessive* to that which is dominant.
- Donor.** One from whom blood or tissue is obtained.
- Dorsal.** Situated at, or relatively nearer to, the back. Opposite of ventral.
- Dorsal Roots (Posterior R., Sensory R.).** Nerve root of vertebrates containing sensory fibers.
- Ductless Gland.** See *Endocrine Gland*.
- Duodenum.** First part of small intestine. Leads out of stomach (junction being guarded by pyloric sphincter).
- Dura Mater.** Firm connective tissue covering brain and spinal cord of vertebrates, containing blood vessels. See *Pia Arachnoid*.
- Dyspnea.** Difficult breathing, or "shortness of breath."
- Ear, Inner (Membranous Labyrinth).** The sense organ of vertebrates which detects position with respect to gravity, acceleration, and sound. Lies inside skull (in auditory capsule) connected by auditory nerve to brain. Consists of two connected sacs containing otoliths. From one (utricle), arise semi-circular canals. From other (saccul), arises organ of hearing (see *Cochlea*). Whole inner ear is filled with a fluid (endolymph).
- Ear, Middle (Tympanic Cavity).** Cavity between ear drum and auditory capsule, present in quadrupeds; communicates with mouth by eustachian tube and is filled with air. Crossed by ear ossicles. Encased in bony projection of skull (bulla).

- Ear Ossicle.** Bone in middle ear, connecting ear drum to inner ear. Transmits vibrations of ear drum caused by sounds to endolymph of inner ear, which in turn affects cochlea. Three bones, malleus, incus, and stapes, are present in mammalian ear.
- Ear, Outer or External.** Part of ear external to ear drum. Ear drum is at inner end of short tube (*external auditory meatus*); this, with the flap of skin and cartilage (pinna) at outer opening of meatus, makes up outer ear.
- Ecology.** Study of the relations of animals and plants to their surroundings, animate and inanimate.
- Ectoderm (*Ectoblast, Epiblast*).** Superficial germ layer of animal embryo, developing mainly into epidermis, nervous tissue, and nephridia (when present). Term is usually applied to the germ layer while it is still a demarcated region of the embryo, after gastrulation, but before differentiation into the derived tissues. Tissues at later stages derived from this embryonic layer may be called ectodermal. See *Germ Layer, Endoderm, Mesoderm*.
- Ectopic.** Out of the normal place.
- Edema.** Swelling of tissue related to increased amount of interstitial fluid.
- EEG (*Electroencephalogram*).** Record of the rhythmical waves of electrical potential occurring in brain, mainly cerebral cortex, which can be detected through intact skull. Patterns in man can be correlated with certain physiological and pathological states.
- Effector.** End organ that normally is activated by impulses reaching it over an efferent nerve.
- Efferent.** Conveying away from, e.g., efferent nerve carries impulses from the central nervous system.
- Elastin.** A fibrous protein in the form of highly extensible and elastic fibers found sparsely scattered in vertebrate connective tissue; numerous in some places, e.g., in lungs, walls of large arteries.
- Electrolyte.** A substance which in solution conducts an electric current; such substances ionize into electrically charged particles.
- Electromotive Force.** The force which by reason of differences in potential causes flow of current from one point to another. It is measured in volts, and is abbreviated E.M.F.
- Electron.** Unit of negative electricity.
- Embolism.** The obstruction of a blood vessel by a clot or other object which has been brought to it by the blood stream.
- Embolus.** A clot or other object which is brought to a blood vessel by the blood stream and there acts as an obstruction to the flow of blood.
- Embryo.** Animal in process of development from fertilized ovum. The embryo is contained in egg membranes, or, in viviparous species, in maternal body.
- Embryology.** Study of development of embryos.
- Emesis.** Vomiting.
- Enamel.** Hard covering of exposed part (crown) of teeth. See *Dentine*.
- Endocardium.** The membrane of endothelial cells lining the heart chambers.
- Endocrine.** Term applied to glands whose function is to secrete active sub-

stances into the blood or lymph; may apply to the secretion itself and in this case is synonymous with hormone.

Endocrine Gland. Gland producing hormones.

Endocrinology. Study of hormones, their production, nature, and actions.

Endoderm (*Entoderm, Endoblast, Entoblast*). Germ layer of animal embryo, composed like mesoderm of cells which have moved from surface of embryo into its interior during gastrulation, developing into greater part of gut with its associated glands, etc. Term is usually applied to the germ layer while it is still a demarcated region of the embryo, after gastrulation, but before differentiation into derived tissues; all tissues at later stages derived from this embryonic layer may be called endodermal. See *Germ Layer, Ectoderm, Mesoderm*.

End Organ. Small organ composed of one or several cells, connected to the CNS by a fiber of the peripheral nervous system. May be a *receptor* or may transform nerve impulses into a stimulus to an effector, e.g., *motor end plates*.

Endothelium. Single layer of smooth flattened cells lining heart, blood vessels, and lymph vessels in vertebrates.

Endothermic Reaction. A chemical reaction which involves the uptake of heat; in general, an energy-storing reaction. Cf. *Exothermic Reaction*.

Enteroceptor. See *Interoceptor*.

Enzyme. An organic substance which has the function of promoting a chemical reaction.

Eosinophil Leucocyte. Polymorphonuclear leucocyte of vertebrates, containing granules staining in acid dyes such as eosin. In human beings, normally about 2-5 per cent of all leucocytes, but become much increased in certain parasitic infections, and in allergies.

Epidermis. In vertebrates, epidermis is several cell layers thick, outermost ones being dead and horny (keratinized) in land-living vertebrates.

Epididymis. Long convoluted tube attached to testis. Receives into one end sperm from testis tubules. Other end leads into vas deferens and so to exterior.

Epiglottis. Flap of mucous membrane and cartilage at base of tongue, on ventral wall of pharynx, against which glottis is pushed and thus closed when swallowing.

Epinephrine. Hormone produced by the adrenal medulla.

Epiphysis. (1) Separately ossified end of growing bone, forming the joint, peculiar to mammalian limb bone and vertebra. Epiphysis is separated from rest of bone (diaphysis) by a plate of cartilage (epiphyseal cartilage). Growth in length of the whole bone occurs by encroachment into this plate of new bone from diaphysis side, and formation of new cartilage on epiphysis side. When growth is complete, epiphysis and diaphysis fuse. (2) A synonym for pineal body.

Epithelium. Sheet or tube of firmly coherent cells, with minimal material between the cells. [The term is, however, often not applied to such sheets or tubes when they have been embryonically derived from mesoderm, e.g., lining of blood vessels (endothelium) or of coelom (mesothelium).] Lines

cavities and tubes and covers exposed surfaces of body, one surface of epithelium being free, other resting, usually, on connective tissue. Its cells are frequently secretory, and secretory part of most glands is made of epithelium.

Equatorial Plate. Arrangement of chromosomes during metaphase of mitosis or meiosis when all lie approximately in one plane at equator of spindle.

Erepsin. Mixture of enzymes (proteases) produced by wall of small intestine; mainly splits peptides (i.e., products of initial protein splitting) to amino acids.

Erythrocyte. See *Red Blood Cell*.

Esophagus. Part of gut between pharynx and stomach.

Estrogen. Any substance producing changes in genital tract characteristic of follicular phase of estrous cycle in various test mammals. Estrogenic activity is usually tested on mouse vagina. An estrogen is normally secreted by mammalian ovary and is responsible for many of the phenomena of the estrous cycle and for development and maintenance of many female sexual characteristics.

Estrogenic. Specifically, the producing of estrus; more generally, it refers to the production of female secondary sexual characteristics and behavior.

Eugenics. Study of possibility of improvement of humanity by altering its genetic composition by encouraging breeding of those presumed to have desirable genes, and discouraging breeding of those presumed to have undesirable genes.

Eupnea. Ordinary quiet breathing such as is seen in a normal person at rest.

Eustachian Tube. Tube connecting middle ear to pharynx. Allows air pressure on inner side of ear drum, i.e., in middle ear, to be equalized with that outside the animal, preventing distortion of ear drum.

Evolution. Cumulative change in the characteristics of populations of organisms, occurring in successive generations related by descent. See *Natural Selection*.

Excretion. Getting rid of products of metabolism or ingested substances which are not used or needed by the body. In animals, particularly applies to products of protein metabolism. Organs mainly concerned are kidneys and bowel.

Exophthalmos. Protrusion of the eyeball.

Exothermic Reaction. A chemical reaction which is associated with liberation of heat. Cf. *Endothermic Reaction*.

Extension. Movement which brings the parts of a limb toward, or into, a straight line; opposite of flexion.

Exteroceptor. Receptor which is stimulated by changes in the external environment; refers usually to receptors in the skin.

Extracellular. Within an organism, but not within its constituent cells. Interstitial. Cf. *Intracellular*.

Eye. Receptor organ for light; utilized in vision.

Eye Muscles. (a) *Extrinsic Eye Muscles.* The set of six muscles which move each eyeball, characteristic of all vertebrates with functional eyes. Supplied

by IIIrd, IVth, and Vth cranial nerves. (See *Oculomotor, Trochlear, Abducens* nerves.) (b) *Intrinsic Eye Muscles*. See *Iris, Ciliary Body*.

Facial Nerve. Seventh cranial nerve of vertebrates. In mammals, mainly motor, going to superficial muscles of face, salivary glands, but also sensory supply to taste buds of front of tongue.

Facilitation. Refers to the process by which the passage of a nerve impulse in a pathway diminishes the "resistance" in the pathway so that a second stimulus evokes the reaction more easily; it is related to summation at synapses.

Fallopian Tube (Uterine Tube). In female mammals, tube with funnel-shaped opening just beside ovary, leading from peritoneal cavity to uterus. One on each side. By muscular and ciliary action, it conducts eggs from ovary to uterus, and sperms from uterus to that place in upper part of tube where they fertilize descending eggs.

Fascia. Connective tissue; applied particularly to sheets thereof. E.g., *superficial fascia* of mammals, the loose connective tissue beneath dermis, containing fat; *deep fascia*, tough sheets enclosing muscles and groups of muscles.

Fat. A compound formed by the union of one molecule of glycerol and three molecules of fatty acid; three molecules of water are produced by the reaction.

Fatty Acid. An organic acid containing only carbon, hydrogen, and oxygen; it consists of a carbon chain which terminates in a COOH group.

Feces. Indigestible residue of food, together with residue of secretions, bacteria, etc., expelled from alimentary canal through anus.

Femur. The thigh bone.

Fertilization. The union of two special cells, the gametes, the essential process of sexual reproduction. The resulting single cell is a zygote.

Fetal Membranes. Extraembryonic membranes of mammal.

Fetus. Mammalian embryo after recognizable appearance of main features of fully developed animal; in man, after about two months of gestation.

Fiber. See *Collagen, Elastin, Nerve, Muscle*.

Fibrillation. Incoordinate contraction of muscle fibers.

Fibrin. See *Blood Clotting*.

Fibrinogen. See *Blood Clotting*.

Fibroblast (Fibrocyte). Kind of cell of irregular branching shape, found distributed throughout vertebrate connective tissue. Function is apparently to form and maintain collagen.

Fibula. The posterior of the two bones (other is tibia) in shank (below the knee) of hind limb of quadrupeds. Lateral bone in lower leg of man.

Filtration. Movement of substances through a membrane as a result of higher pressure on one side of the membrane.

Fistula. An abnormal opening or tract.

Flexion. Bending of parts of a limb at the joint, i.e., movement away from a straight line; opposite of extension.

Follicle. A little sac.

Follicle-Stimulating Hormone. F.S.H. The hormone of the anterior pituitary lobe which stimulates the Graafian follicles of the ovary, induces follicular maturation and the liberation of estrin. In the male, it stimulates the epithelium of the seminiferous tubules inducing spermatogenesis.

Foramen. A hole or perforation, especially a hole in bone.

Fovea. Shallow pit in retina which is place of greatest acuity of vision. Contains no rods, but very numerous cones; there are no blood vessels, and no thick layer of nerve fibers interposed between cones and incoming light as in rest of retina.

Fraternal Twins. See *Dizygotic Twins*.

Frontal Bone. Large bone covering front part of brain (region of forehead in man). Air spaces extend from nasal cavity into frontal bones of mammals (*frontal sinuses*).

Fructose (Levulose). A 6-carbon-atom sugar (hexose). Combined with glucose in sucrose. Widely distributed in plants.

Galactose. A hexose sugar; obtained by digestion of lactose.

Gall Bladder. Small sac arising from bile duct near liver. Stores bile.

Galvanometer. An instrument for measuring quantity of electric current (i.e., amperes).

Gametes. The ova and spermatozoa. The germ cells which unite to form a zygote.

Gametocyte. Cell which undergoes meiosis, forming gametes. See *Oöcyte*, *Spermatoocyte*.

Ganglion. A mass of nerve cell bodies usually located outside the central nervous system. The term is derived from a Greek word meaning knot.

Gastric. Of the stomach.

Gastrula. Stage of embryonic development of an animal, succeeding blastula. See *Gastrulation*.

Gastrulation. Embryological term for the complex of cell movements which occurs in almost all animals at the end of the cleavage period. The movements carry those cells whose descendants will form the future internal organs from their largely superficial position in the blastula (q.v.) to approximately their definitive positions inside the embryo. In many embryos, these presumptive internal organs undergo gastrulation in two main groups of cells, endoderm (future gut, etc.), and mesoderm (future muscles, blood, etc.). The ectoderm (future external layer, and also the future nervous system, which later becomes internal) is also rearranged during the gastrulation movements to approximately its definitive position.

Gene. A unit in the chromosome which carries the transmissible characteristics.

Genetics. Study of heredity and variations and of the resemblances and differences between organisms. See *Gene*.

Genotype. Genetic constitution (the particular set of allelomorphs present in each cell of an organism), as contrasted with the characteristics manifested by the organism (*phenotype*, q.v.).

Genus. One of the kinds of groups used in classifying organisms. Consists of a number of similar species; occasionally of one species only. Similar genera are grouped in a family. See *Binomial Nomenclature, Classification*.

Germ Cells. See *Gametes*.

Germ Layer. One of the main layers or groups of cells which can be distinguished in an embryo during and immediately after gastrulation (q.v.). These layers are roughly similar in arrangement and in ultimate differentiation in most animals. There are two in diploblastic animals, endoderm (q.v.) and ectoderm (q.v.). In triploblastic animals, there is in addition the mesoderm (q.v.). There is general agreement as to which layer gives rise to which tissues, e.g., nervous tissue is characteristically ectodermal, cartilage both mesodermal and ectodermal.

Gestation. Pregnancy.

Gestation Period. Length of time from conception to birth in viviparous animal.

Gland. An organ whose main function is to build up one or more specific chemical compounds which are passed to the outside of the gland. Some glands are *exocrine*, i.e., their secretions are discharged, usually through a tube or *duct*, on to a surface, either the outer (epidermal) surface of the body, e.g., sweat glands of mammals, or the inner surface of the gut, e.g., digestive glands. *Endocrine glands* secrete hormones which are carried in the blood.

Glenoid Cavity. Cup-like hollow on scapula into which head of humerus fits, forming shoulder joint.

Glia (Neuroglia). Supporting tissue of vertebrate central nervous system, consisting mainly of cells with long fibrous processes, derived from embryonic neural tissue, and mesodermal cells (microglia) closely similar to macrophages.

Globulins. Group of proteins, heat-coagulable, soluble in dilute salt solution, but not in water. Present in cells and blood plasma.

Glomerulus. A tuft or cluster; used to designate the tuft of vessels which is found at the expanded end of the renal tubule.

Glossopharyngeal Nerve. Ninth cranial nerve. Mainly concerned with both sensory and motor aspect of the swallowing reflex, and taste buds of back of tongue.

Glottis. Opening of trachea into pharynx. Can usually be closed by muscles. In mammals, opening between vocal chords. See *Larynx, Epiglottis*.

Gluconeogenesis. Formation of glucose from non-carbohydrate sources, especially from protein.

Glucose (Dextrose). A 6-carbon-atom sugar (hexose) widely distributed in plants and animals, particularly in compounds as disaccharides, e.g., sucrose, and polysaccharides, e.g., starch, cellulose, glycogen. Splitting of glucose, ultimately to CO_2 and water, involving intermediary combining with phosphate is a major energy source for metabolic processes. In green plants, glucose is a product of photosynthesis, from CO_2 and water; it is stored as starch. In animals, glucose is obtained mainly from digestion of disaccharides

and polysaccharides and by synthesis from glycerol and residues of deaminated amino acids. It is stored as glycogen. See *Blood Sugar*.

Glycerol. $\text{CH}_2\text{OHCHOHCH}_2\text{OH}$, a trihydroxy alcohol released by hydrolysis of fat.

Glycogen. A soluble polysaccharide built up of numerous glucose molecules. Carbohydrate is stored by animals as glycogen. Present especially in liver and muscles.

Glycolysis. Breakdown of glucose into lactic acid, involving a complex system of enzymes and coenzymes.

Glycosuria. Presence of glucose in the urine.

Gnathostomata. Vertebrates with jaws. A grouping of vertebrate classes sometimes used in classification as a subphylum in contrast to Agnatha.

Goblet Cell. Pear-shaped cell, present in some epithelia, the part near the free surface of the epithelium being swollen with mucin, which may be secreted on to the surface.

Golgi Apparatus (Golgi Body, Golgi Material). Local clump of material present in cytoplasm of most animal cells, probably normally in the form of fatty globules or fat-enveloped vacuoles. It can be blackened by staining technics using silver or osmium, and then often appears as a network. Function unknown, but often seems associated with formation of secretions.

Gonad. Organ of animals which produces gametes. In vertebrates, produces hormones too. See *Ovary, Testis*.

Gonad Hormone. One of sex hormones produced by gonad. See *Androgen, Estrogen, Progesterone*.

Gonadotrophic (Gonadotropic) Hormones (Gonadotrophins). Hormones secreted by anterior lobe of pituitary of vertebrates, and by mammalian placenta, which control activity of gonads. See *Follicle-Stimulating Hormone, Luteinizing Hormone*.

Graafian Follicle. Fluid-filled spherical vesicle in mammalian ovary containing an oöcyte attached to its wall. Growth of follicles is under influence of pituitary gland. See *Follicle-Stimulating Hormone*. Cells of follicle are probably main site of estrogen production of ovary. After ovulation, follicle becomes corpus luteum (q.v.).

Granulocyte. See *Polymorph*.

Gray Matter. Tissue of vertebrate central nervous system containing numerous cell bodies, dendrites of nerve cells, and terminations of nerve fibers forming synapses with these together with glia and blood vessels. Occurs mainly as an inner layer surrounding central canal, but occurs also as a superficial layer (cortex) on cerebellum and cerebral hemispheres in some vertebrates. It is the tissue of the nuclei or centers. Cf. *White Matter*.

Gut. The alimentary canal.

Hair. Characteristic of mammal. Each hair consists of numerous cornified epidermal cells growing out from its base in hair follicle where active cell division occurs.

- Hair Follicle.** Deep pit of mammalian epidermis surrounding root of hair which projects far down into dermis. Receives duct of sebaceous gland.
- Hallux.** "Big toe" of pendactyl hind limb. On inner (tibial) side.
- Haploid.** Having a single set of unpaired chromosomes in each nucleus. Characteristic of gametes.
- Haversian Canals.** Channels (roughly 50μ diameter) carrying blood vessels and nerves, which ramify throughout bone, communicating with its surface and marrow. Sheets (lamellae) of bone, and bone cells, are arranged concentrically around the canals.
- Heart.** Muscular organ of vascular system, pulsations of which move blood. See *Auricle, Ventricle*.
- Hematocrit.** The per cent volume of cells in a unit volume of blood. It is normally around 45 per cent.
- Hemiplegia.** Paralysis of one side of the body.
- Hemodynamics.** The study of the forces concerned in the movement of blood through the heart and blood vessels.
- Hemoglobin.** Respiratory pigment (q.v.) occurring in blood and some muscles of vertebrates. A protein with iron in the prosthetic group; closely related to chlorophyll and to cytochrome.
- Hemolysis.** The liberation of hemoglobin from the erythrocytes.
- Hemophilia.** Hereditary disease characterized by delayed clotting of the blood and hence by frequency of severe hemorrhage.
- Hemopoiesis (Hematopoiesis).** Formation of blood corpuscles. Occurs in lymphoid tissue and bone marrow of vertebrates.
- Hemopoietic.** Pertaining to or concerned with the production of blood cells.
- Heparin.** Substance which prevents blood clotting. Extractable from various tissue such as liver and lung. Probably produced in most cells which occur in connective tissue. It is a sulfur-containing complex polysaccharide.
- Hepatic.** Of the liver.
- Hepatic Portal System.** System of veins carrying blood from capillaries of intestine to liver. Absorbed products of digestion (except fats, see *Lacteals*) thus are carried straight to liver cells which transform them chemically. See *Deamination*.
- Heterozygous.** Having different genes in the two corresponding loci of a pair of chromosomes (q.v.). Cf. *Homozygous*.
- Hexose.** A sugar having a six-carbon chain; general formula $C_6H_{12}O_6$.
- Hindbrain.** Hindmost of the three divisions marked out by constrictions in the embryonic vertebrate brain. Becomes during development medulla oblongata and cerebellum.
- Hip Girdle (Pelvic Girdle).** In tetrapods (except the earliest Amphibia), ischiopubis forms two bones, an anterior pubis and posterior ischium, and the ilium unites with one or more sacral vertebrae (compare shoulder girdle), forming a complete girdle round body in this region and giving rigid support to hind limbs for locomotion. See *Acetabulum, Innominate Bone*.
- Hirsutism.** Abnormal hairiness.

- Histamine.** Organic base, released from tissues when they are injured, causing dilation of local blood vessels.
- Histiocyte.** Resting, connective-tissue form of macrophage.
- Histology.** The study of the structure of tissues.
- Homeostasis.** Maintenance of constancy of internal environment (q.v.).
- Homo.** Genus of catarrhine primates whose only living representative is man (*Homo sapiens*). *H. sapiens* is distinguished anatomically by large brain (about 1500 cc.); absence of prominent brow ridges; chin prominence; teeth in each jaw arranged in a smooth curve, with small canines; foot very different from hand, with reduced toes, big toe not opposable to others. Distinguished in behavior by walking upright, by using tools with hands, and by speech.
- Homoiotherm.** "Warm-blooded." Maintaining a constant body temperature, usually above that of surroundings. Characteristic of birds and mammals.
- Homologous.** An organ of one animal is said to be homologous with an organ of another when both have a fundamental similarity of structure and/or position relative to other organs, manifested especially during the embryonic period regardless of their functions in the adult, which may be very different. The similarity is assumed to be due to descent of the organisms from a common ancestor. The presumption is that a developmental process occurring in a common ancestor has become modified in two or more different directions in the descendant species, without the divergence obscuring the common origin. Homology of organs implies relationship of the organisms bearing the organs, and it is the main concept of evolutionary comparative anatomy. Cf. *Analogous*.
- Homozygous.** Having identical genes (i.e., not having different allelomorphs) in the two corresponding loci of a pair of chromosomes (q.v.). Cf. *Heterozygous*.
- Hormonal.** Of the nature of hormones.
- Hormone.** A substance produced in a gland and liberated into the blood or lymph to exert specific effects in the body.
- Humerus.** Bone of upper arm.
- Humoral.** Pertaining to active substances in the body, similar in meaning to hormonal.
- Hunger Contractions.** Rhythmical contractions of empty stomach which give rise to feeling of hunger.
- Hybrid.** Plant or animal resulting from a cross between parents that are genetically unlike (i.e., heterozygous) with regard to a given trait. Term often is restricted to the offspring of two different species or of well-marked varieties within a species.
- Hydrostatic Pressure.** Pressure exerted at the bottom of a column of liquid due to the weight of the liquid. It may be expressed in terms of the height of the column, whether it be water or another liquid such as mercury.
- Hyperglycemia.** Elevated level of blood sugar.
- Hypermetropia.** Farsightedness.

Hyperplasia. Increase in amount of tissue by increase in number of cells which individually keep their usual size (cf. *Hypertrophy*), e.g., when part of liver is removed, remainder undergoes hyperplasia.

Hyperpnea. Increased pulmonary ventilation.

Hypertension. Abnormally high arterial blood pressure.

Hypertonic. In the case of solution, the term refers to a concentration greater than that of the body fluids, i.e., greater than isotonic (q.v.).

Hypertrophy. (1) Increase in size of tissue or organ by increase in size of individual elements (cells or collagen fibers) without increase of their numbers (cf. *Hyperplasia*), e.g., in exercised muscle. (2) Sometimes, increase in size of tissue or organ, mechanism unspecified, but often hyperplasia. See *Compensatory Hypertrophy*.

Hypoglossal Nerve. Nerve supplying muscles of tongue and those below pharynx. Twelfth cranial nerve.

Hypoglycemia. Low level of blood sugar.

Hypophysectomy. Removal of the pituitary body or *hypophysis cerebri*.

Hypophysis. Synonymous with pituitary body (q.v.).

Hypotension. Low arterial blood pressure.

Hypothalamus. Floor and sides of brain just behind attachment of cerebral hemispheres. Derived from forebrain. Portion of brain below the thalamus. In mammals, known to contain centers coordinating, among other things, manifestations of rage and mechanism of body temperature control, both of which predominantly involve autonomic nervous system. Pituitary is immediately below hypothalamus.

Hypotonic. Said of solutions which are of less than isotonic concentration.

Hypoxia. See *Anoxia*.

Identical Twins. See *Monozygotic Twins*.

Ileum. That part of small intestine of mammals preceding the large intestine.

Ilium. Dorsal part of hip girdle, which in tetrapods is jointed to one or more sacral vertebrae.

Immunity. Ability of an animal to resist infection by parasitic organisms. Immunity of animals is due to many different mechanisms; however, since great attention has been given to defence by antibodies, which can be artificially induced to appear in the body, the term immunity is often restricted to that due to antibodies.

Impulse. The "message" which is conducted along a nerve fiber. It is a travelling wave of chemical and physical events involving particularly the surface membrane of the fiber.

Incisor. Chisel-shaped tooth in front of mouth of mammals. All teeth on premaxilla of upper jaw and those biting against them in lower jaw are incisors.

Incus. Mammalian ear ossicle.

Inductorium. Instrument for producing induced electric currents, used for stimulating irritable tissues.

Inflammation. The local response to any local injury in a vertebrate. Consists of (1) dilation of blood vessels, (2) invasion by leucocytes, (3) passage of

blood proteins and fluid through capillary walls into tissue spaces. Functions probably as protective mechanism (by means of leucocytes and antibodies) against any invading bacteria.

Inhibition, Nervous. Prevention, as a result of the influence of nerve impulses, of activation of an effector. May occur in central nervous system, e.g., when a muscle is stimulated by its motor nerve fibers to contract, the tonus of antagonistic muscles is simultaneously relaxed by inhibition of their motor nerve cells (*reciprocal inhibition*). Such central inhibition is one of the most important ways in which the central nervous system, by preventing action of effectors in unsuitable circumstances, produces its flexible control of activities.

Innervation. Nerve supply (to a particular organ).

Innominate. (1) Short artery arising from aorta and giving rise to a subclavian artery (to forelimb) and a carotid artery (to head), in many birds and mammals. (2) *I. bone.* Each lateral half of the hip girdle, when pubis, ilium, and ischium are fused into a single bone, as in adult reptiles, birds, and mammals.

Insulin. Hormone controlling amount of glucose in the blood; secreted by islets of Langerhans in pancreas. Secretion is stimulated by high glucose concentration in blood, which insulin decreases by suppressing breakdown of liver glycogen to glucose, and encouraging building up of muscle glycogen from glucose. Antagonized by epinephrine. See *Blood Sugar*.

Intercellular. Between the cells. *I. fluid* (interstitial fluid, tissue fluid), fluid between tissue cells of animals, bathing the plasma membranes (to be distinguished from blood; see *Internal Environment*). *I. material* is chiefly skeletal, e.g., reticulin, collagen, elastin, bone salts, matrix of cartilage and connective tissue, cement substance between epithelial cells. *I. spaces*, spaces filled with interstitial fluid.

Internal Environment. Medium in which body cells are bathed, i.e., the interstitial fluid. In equilibrium with blood stream in vertebrates, it is normally kept highly constant in composition (homeostasis), e.g., in respect of osmotic pressure, content of individual ions, acidity and alkalinity (pH), and glucose concentration, by sensitive mechanisms which control these conditions in the blood, and hence in the interstitial fluid.

Interoceptor. (1) Receptor which detects stimuli arising inside the body. Cf. *Exteroceptor*. (2) In more restricted sense, excluding proprioceptors detecting position and movement. (3) In more restricted sense still, receptor in lining of gut and respiratory organs, detecting stimuli from substances introduced from outside.

Interphase. Resting stage of nucleus.

Interstitial. Pertaining to the interspaces of the tissues, e.g., interstitial fluid is found between the cells.

Interstitial Cells. Of vertebrate gonads; those which lie between the ovarian follicles or between the testis tubules. Those of the testis probably secrete the testicular sex hormones (chiefly testosterone).

Interstitial Fluid. See *Intercellular Fluid*.

Intestine. Alimentary canal between stomach and anus.

Intracellular. Within a cell.

Invertase. See *Sucrase*.

In Vitro. Applied to biological processes when they are experimentally made to occur in isolation from the whole organism. E.g., the activities of cells in tissue culture occur *in vitro*. Cf. *In Vivo*.

In Vivo. Within the living organism. Cf. *In Vitro*.

Ion. An atom or chemical radical having a positive (cation) or negative (anion) electrical charge.

Ionization. The dissociation of a substance into ions.

Iris. Structure controlling amount of light admitted to eye. Iris is the colored part of human eye. It is a thin sheet of tissue, forming a pigmented diaphragm in front of lens with central opening (pupil) through which light passes to retina. Attached at outer margin to ciliary body (q.v.). Contains radiating muscles which enlarge pupil (controlled by sympathetic nerves) and a ring of muscles at its free inner margin which narrows pupil (controlled by parasympathetic nerves). Light, stimulating retina, reflexly controls size of pupil, narrowing for strong, enlarging for dim light. Accommodation for near vision is also accompanied by narrowing.

Irritability. Responsiveness to change in environment.

Ischium. Ventral, backward-projecting part of hip girdle. Ischia bear the weight of a sitting primate.

Islets of Langerhans. Groups of cells, scattered throughout pancreas, which secrete insulin.

Isometric. Said of a muscular contraction characterized by increased tension without change in length of the muscle; literally means "same measure."

Isosmotic. Having the same osmotic tension.

Isotonic. (1) Said of solutions which have the same osmotic tension as the body fluids. E.g., 0.9 per cent NaCl solution is approximately isotonic. (2) Refers to shortening of muscle without change in tension. See *Isometric*.

Jaundice. Yellow discoloration of the skin and mucous membranes produced by bile pigment.

Jejunum. Part of small intestine succeeding duodenum and preceding ileum.

Jugular. Main vein returning blood from head.

Katabolism. See *Catabolism*.

Keratin. Tough fibrous protein containing much sulfur, occurring in epidermis (forming resistant outermost layer of skin) hair and nails.

Keratinization. Transformation of epidermal cells in keratin.

Ketogenic. Capable of being converted into, or causing production of, ketones.

Ketone. A compound containing the $\begin{array}{c} | \\ \text{C}=\text{O} \\ | \end{array}$ group. See *Acetone*.

Kidney. Organ concerned with excretion and with regulation of plasma composition. Consists of numerous nephrons and their blood supply.

Kilogram Calorie. See *Calorie*.

Kinesthetic. Detecting movement. Refers, e.g., to sense organs of muscles, tendons, and joints. See *Proprioceptor*.

Krebs Cycle. Complex cycle of enzyme-controlled reactions by which pyruvic acid is broken down in presence of oxygen to carbon dioxide. The cycle provides the final step in oxidation of carbohydrates, since glycogen and glucose are broken down to pyruvic acid. It also deals with the final phases of fat oxidation and is concerned in synthesis of some amino acids.

Kymograph. An instrument consisting of a drum arranged to revolve so as to record movements of some type of lever.

Labial. Of the lip.

Labyrinth, Membranous. See *Ear, Inner*.

Lachrymal Gland. Tear gland of eye. Lies beneath upper eyelid. Continually secretes small amounts of tears which keep cornea moist. Tears drain into nose through lachrymal duct from inner corner of eye.

Lactase. Enzyme which digests lactose.

Lactation. Production of milk. See *Mammary Gland, Lactogenic Hormone*.

Lacteals. Lymph vessels draining villi of intestine. Into them passes fat absorbed from intestine, and the fat globules give milky appearance to contained lymph.

Lactic Acid. Organic acid formed as product of splitting up of glucose, which is an essential process in utilization of energy of food by many animal cells, and particularly during contraction of skeletal muscle.

Lactogenic Hormone. Hormone of anterior pituitary, probably largely responsible for onset of milk production in mother after parturition. Also called prolactin.

Lactose. Sugar (disaccharide, with twelve carbon atoms) occurring in mammalian milk. Compound of a molecule of glucose and a molecule of galactose (into which it is split by intestinal enzyme *lactase*).

Larynx. Dilated region of upper part of trachea, just at its junction with pharynx ("Adam's apple"). Has plates of cartilage in its walls, movable by muscles which open and close glottis. A dorso-ventral fold of membrane (vocal cord), situated within larynx, projects into its lumen from each side wall. Vibration of cords produce vocal sounds.

Latent Period. Time between application of stimulus and first detectable response in an irritable tissue, e.g., muscle or nerve. Also applied to a reflex. Term *reaction time* is more often used for reactions of a whole animal.

Lemniscus. A fillet; a narrow ribbon of nerve fibers.

Lens. Of eye, transparent structure just behind pupil lying in aqueous humor, attached by collagen fibers to ciliary body. Not as important as cornea in the refraction which produces image on retina; function is accommodation by change of thickness.

Leucocyte. See *White Blood Cell*.

Leucocytosis. Increase in number of white blood cells.

Ligament. Strong band of collagen connecting the two bones at a joint. Helps

restrict movement to that provided for by shape of joint, preventing dislocation.

Lingual. Of the tongue.

Linkage. Association of two or more non-allelomorphic genes, so that they tend to be passed from generation to generation as an inseparable unit, and fail to show independent assortment. Separation of such genes into different chromosomes occurs from time to time as a result of crossing-over.

Linoleic Acid. Unsaturated fatty acid required by mammals, probably including man.

Lipase. Enzyme which splits esters of fatty acids, e.g., true fats, into alcohol and acid.

Lipid. Any of a group of substances which includes fats, fatty acids, soaps, sterols, and related compounds.

Lipoid. (1) Substance resembling fat in solubility, but not containing fatty acid (e.g., steroid, carotene); (2) substance resembling fat in solubility, which may contain fatty acid, but excluding neutral fats; (3) occasionally refers to fat as such as well as related compounds.

Liver. Large gland whose duct opens into duodenum. Situated in contact with lower surface of diaphragm on the right side.

Lumbar Vertebrae. Vertebrae of the waist region; without ribs; between the rib-bearing thoracic and the sacral vertebrae.

Lumen. Cavity. Space within a tube or sac.

Lung. Organ for breathing air. See *Bronchus*, *Bronchiole*, *Alveolus*.

Luteal Tissue. Tissue which fills cavity of a ruptured Graafian follicle, constituting a corpus luteum. Derived from follicle cells. Secretes progesterone.

Luteinizing Hormone (LH). A gonadotropic hormone secreted by anterior lobe of pituitary which stimulates ovulation and formation of the corpus luteum (q.v.) in females and secretion of androgen in males. See *Follicle-Stimulating Hormone*.

Lymph. Fluid drained by lymph vessels from intercellular spaces; its water content ultimately derived from blood by filtration through capillary walls. Colorless, containing small amount of protein and varying numbers of cells, chiefly lymphocytes. See *Lymphatic System*.

Lymphatic (Lymphatic Vessel). Lymph-carrying vessel, lined by smooth endothelium like a blood vessel, but always with thin walls, which in larger vessels contain smooth muscle and connective tissue. Many have valves. See *Lymphatic System*, *Lacteals*.

Lymphatic System. System of fluid-containing tubes. A network of small tubes (lymph capillaries) permeates most tissues (not nervous system), and joins to form ever larger vessels (but not usually larger than 2-3 mm. diameter) which finally join venous system. Lymph is drained from the interstitial spaces into the blood by this system.

Lymph Node (Lymph Gland). Organ on the course of a main lymphatic, consisting of lymphoid tissue. Its macrophages remove foreign bodies from lymph. If these foreign bodies are bacteria, it may become inflamed and swollen. It is an important source of antibodies.

Lymphocyte. Kind of white blood cell. Rather small (6–8 microns diameter), but with relatively large spherical nucleus. Forms 20–25 per cent of white blood cells. Non-phagocytic, ameboid, probably produces or carries antibodies. Lymphocytes are continuously produced in lymphoid tissue and each lymphocyte has a short life.

Lymphoid Tissue (Lymphatic Tissue). Tissue of vertebrates which produces lymphocytes by division of some of its cells; it also contains macrophages. Widely distributed in body. Occurs especially in spleen, lymph nodes, thymus, adenoids, and tonsils.

Macrogamete (Megagamete). Female gamete, distinguished from male gamete by larger size and/or by structure.

Macrophages. Phagocytic cells widely distributed in body. Occur in all connective tissue, where after injury they become active in removing the debris. The resting, connective tissue forms are often called *histiocytes*. Occur also (forming the reticulo-endothelial system) in contact with lymph (in lymph nodes) or blood (in bone marrow, spleen, liver), removing from these fluids any foreign particles. Move by membrane-like pseudopodia. See *Reticulo-Endothelial System, Monocyte*.

Malleus. First of three mammalian ear ossicles activated by entering sound waves (hammer).

Malpighian Body (Malpighian Corpuscle). Filtering unit of vertebrate kidney; a Bowman's capsule with its glomerulus.

Maltase. See *Maltose*.

Maltose. Sugar (disaccharide, with twelve carbon atoms) formed as a result of starch breakdown. A maltose molecule is a compound of two molecules of glucose (into which it is split by enzyme *maltase*).

Mamma. See *Mammary Gland*.

Mammal. Any member of the Mammalia, a class of tetrapod vertebrates, e.g., man, dog, whale. Contains three living subclasses, Monotremata, Marsupialia, and Placentalia. Peculiar to mammals are: hair, milk secretion, diaphragm used in respiration, lower jaw of single pair of bones, presence of only left systemic arch, three bones (auditory ossicles) in each middle ear connecting ear drum and inner ear.

Mammary Gland. Milk-producing gland on ventral surface, peculiar to female mammals. Growth and activity is affected by hormones.

Mandible. Lower jaw.

Manus. Hand. Carpus, metacarpus, and digits of tetrapod forelimb. See *Pentadactyl Limb, Pes*.

Mastoid Process. Excrescence of human skull (or periotic bone) just behind ear, containing air spaces which communicate with middle ear.

Maturation of Germ Cells. Process of development of mature sperm and ova from cells in testis and ovary respectively. It includes (1) reduction division (or meiosis) of the nucleus, which halves the number of chromosomes and (2) extensive changes in cytoplasm, which are quite different in the two sorts of gametes. See *Oöcyte, Spermatocyte*.

Maxilla. (1) One of the bones of the upper jaw of vertebrates (and of the face in man) which carries all of the upper teeth except incisors. (2) Sometimes used for the whole upper jaw of vertebrates.

Meatus. A passage, e.g., external auditory meatus (see *Ear, Outer*).

Meconium. Contents of intestine of mammalian fetus. Derived from secretions of glands discharging into gut, and swallowed amniotic fluid.

Median. Situated in or towards the plane which divides a bilaterally symmetrical organism or organ into right and left halves.

Mediastinum. The region between the two pleural cavities. It contains the heart, aorta, esophagus, etc.

Medulla. See *Medulla Oblongata*.

Medulla Oblongata. Often called simply medulla. Most posterior part of the brain, merging into the spinal cord. Thick walled and floored, but with thin roof. Its internal cavity is fourth ventricle. Contains important centers for respiratory movement, control of blood vessels and heart, etc. Glossopharyngeal and vagus nerves arise from it.

Medullated Nerve Fiber. Synonym of myelinated nerve fiber. See *Nerve Fiber*.

Meiosis (Reduction Division). See *Oögenesis, Spermatogenesis*.

Melanin. Dark-brown pigment present in many animals which in different concentrations gives brown and yellow coloration. Color of human hair is due mainly to melanin.

Membranous Labyrinth. See *Ear, Inner*.

Mendelism. Science of the behavior of genes in inheritance, studied by breeding experiments.

Meninges. Membranes covering the central nervous system; dura mater (q.v.) outside pia arachnoid (q.v.).

Menstrual Cycle. Modified estrous cycle of catarrhine primates (Old World monkeys, anthropoid apes, and man) which has special feature of sudden destruction of mucosa of uterus at end of progestational phase of cycle, producing bleeding; and absence of any well-marked period of estrus.

Mesenchyme. Embryonic connective tissue consisting of rather widely scattered, irregularly branching cells in a jelly-like matrix. Gives rise to connective tissue, bone, cartilage, blood, etc.

Mesentery. (1) Double layer of peritoneum attaching stomach, intestines, spleen, etc., to dorsal wall of peritoneal cavity. Contains blood, lymph, and nerve supply to these organs. (2) More strictly, the same fold attaching small intestine only.

Mesoderm (Mesoblast). Germ layer of triploblastic animal embryo composed, like endoderm, of cells which have moved from surface of embryo into its interior during gastrulation, developing into tissues between gut and ectoderm (muscle, blood, connective tissue, etc.). Term is usually applied to the germ layer while it is still a demarcated region of the embryo, after gastrulation, but before differentiation into the derived tissues, and all the tissues at later stages derived from the embryonic layer may be called mesodermal. See *Germ Layer, Ectoderm, Endoderm*.

Mesothelium. Layer of flattened cells, a simple squamous epithelium in appear-

- ance, derived from mesoderm; lines coelomic cavities of vertebrates (see *Pericardium*, *Pleura*, *Peritoneum*) and some other spaces, e.g., synovial sacs.
- Metabolism.** (1) In general, the chemical processes occurring within an organism. They involve breaking down of organic compounds from complex to simple (catabolism) with liberation of energy available for the organism's many activities; and building up of organic compounds from simple to complex (anabolism) using energy liberated by catabolism. (2) Metabolism of some constituent of an organism (e.g., "fat metabolism"); the part of total metabolism involving that constituent.
- Metabolism, Basal.** The rate of energy expenditure of an animal at rest, but not asleep (BMR), is expressed as the output of Calories per square meter of body surface per hour. Measured directly, or indirectly by calculation from the amount of oxygen consumed or carbon dioxide given off.
- Metabolite.** Substance which takes part in a process of metabolism (q.v.). Most metabolites are made by the organism in the course of metabolism; others, however, must be taken in from the environment.
- Metacarpal Bones.** Bones of the forefoot of tetrapod vertebrates (palm region of man). Rod-like bones, usually one corresponding to each digit. Articulate with wrist bones (carpals) proximally, finger bones (phalanges) distally.
- Metacarpus.** Region of forefoot of tetrapods, containing metacarpal bones. Palm region of man.
- Metaphase.** Stage of mitosis (q.v.) or meiosis (q.v.) when chromosomes are arranged on equator of spindle.
- Metaplasia.** Transformation of one sort of normal adult tissue into another.
- Metatarsal Bones.** Bones in the hindfoot of tetrapod vertebrates. Rod-like bones, usually one corresponding to each digit. Articulate with ankle bone (tarsals) proximally, toe bones (phalanges) distally.
- Metatarsus.** Region of hindfoot of tetrapods containing metatarsal bones.
- Metazoa.** Animals whose bodies consist of many cells, as distinct from the Protozoa which are unicellular; all animals commonly recognized as animals, including man.
- Microbe.** Microscopic organism, usually pathogenic.
- Microgamete.** Male gamete, differentiated from female gamete by smaller size and/or by structure. Cf. *Macrogamete*.
- Micron.** Unit of length for microscopic objects. One thousandth of a millimeter. Usually written, μ . The limit of resolution of a microscope using visible light is about one-fifth of a micron. A millimicron, one thousandth of a micron, is written $m\mu$, and is ten Angstroms (the physicists' unit of small distance).
- Micturition.** Urination.
- Midbrain (Mesencephalon).** Middle of the three divisions marked out by constrictions in the embryonic vertebrate brain. Becomes during development very thick walled, with small central cavity. Particularly concerned with sight and hearing.
- Middle Ear.** See *Ear, Middle*.
- Milk Teeth.** See *Deciduous Teeth*.

- Mitochondria (Chondriosomes).** Minute semisolid bodies, numbers of which occur in the cytoplasm of every cell (except Bacteria and blue-green Algae). Enclosed in a membrane and have a complex internal structure. Rod shaped or granular (name mitochondria sometimes restricted to latter); approximately $\frac{1}{4}$ –1 micron width or diameter. Stain specifically in the living cell with Janus Green. Made of protein and fat and contain enzymes.
- Mitosis.** Cell division in which the daughter cells have the same number of chromosomes as the parent cells. See *Meiosis*.
- Mitral Valve.** Valve between left auricle and left ventricle of mammalian heart, consisting of two membranous flaps, hence known as bicuspid valve.
- Molars.** Crushing back teeth of mammals which, unlike premolars, have no predecessors in the milk teeth. They have usually several roots, and a complicated pattern of ridges and projections on biting surface. See *Dental Formula*.
- Molecule.** A chemical combination of two or more atoms which form a specific substance.
- Monocyte.** Largest kind of white blood cell (9–12 microns diameter). Has spherical nucleus. Form 3–8 per cent of white blood cells. Actively phagocytic when, in inflammation, they invade the tissues. Identical with, or closely related to, macrophages.
- Monosaccharide.** A simple sugar; includes the hexoses ($C_6H_{12}O_6$) and pentoses ($C_5H_{10}O_5$).
- Monozygotic Twins (Identical Twins, Uniovular Twins).** Twins due to fission into two, at an early stage of its development, of the embryo derived from a single fertilized egg. Such twins are genetically identical. Cf. *Dizygotic Twins*.
- Morphology.** Study of structure.
- Morula.** Embryo during process of cleavage, before blastula stage; consists of a number of blastomeres.
- Motor.** Concerned with stimulation of effector organs. *M. cortex.* Part of cerebral cortex controlling nerves to skeletal muscles. *M. end plate.* End organ of a motor nerve fiber on a muscle fiber, consisting of an accumulation of muscle cytoplasm and nuclei, within which the nerve fiber branches, and through which its nerve impulses stimulate the muscle fiber. *M. nerve.* Peripheral nerve consisting of nerve fibers of motor neurons. *M. nerve fiber.* Nerve fiber of motor neuron. *M. neuron (motoneuron).* Nerve cell whose nerve fiber connects with effector organ; conducts impulses from central nervous system which stimulate effector to activity. See *Nerve-Root*.
- Motor Root.** Nerve root, synonymous with ventral root (q.v.).
- Mucin.** Mucoprotein forming mucus in solution.
- Mucoproteins (Glycoproteins).** Compounds of certain carbohydrates with protein, e.g., mucin, matrix of cartilage.
- Mucosa.** See *Mucous Membrane*.
- Mucous Membrane.** General name for a moist epithelium and its immediately underlying connective tissue in vertebrates. Particularly applied to lining of gut and urinogenital ducts. Epithelium is usually simple, though stratified

- near opening to exterior; often ciliate; often contains goblet cells secreting mucus.
- Mucus.** Slimy solution of mucin secreted by goblet cells of vertebrate mucous membrane.
- Muscle.** Tissue consisting of cells which are highly contractile.
- Mutant.** Gene which has undergone mutation within the particular stock of organisms under observation; or organism bearing such a gene; or character due to such a gene.
- Mutation.** Sudden and relatively permanent chromosomal change. The most important mutations are those occurring in the gametes, since they can produce an inherited change in the characteristics of the organisms developing from them, such changes providing a basis for evolution.
- Myelin.** Fatty substance (phospholipid, cholesterol, etc.) with protein, making a sheath to larger nerve fibers of vertebrates.
- Myeloid Tissue.** Tissue producing myeloid elements (polymorphs and red blood cells) of blood, which are formed throughout life. Except in embryo, usually located in bone marrow. In adult man, mainly in ribs, sternum, skull, pelvic girdle, vertebrae.
- Myocardium.** The heart muscle.
- Myopia.** Nearsightedness.
- Myosin.** See *Actomyosin*.
- Myotome.** That part of somitic mesoderm (q.v.) which forms striated muscle.
- Nares.** Nostrils.
- Nasal Cavity.** Cavity of head containing olfactory organ; communicating with mouth and with exterior by internal and external nares respectively. See *Palate*.
- Native Protein.** Protein in its naturally occurring state, i.e., not denatured.
- Natural Selection.** The principal mechanism of evolutionary change, originally suggested by Darwin in 1859. The theory that evolution occurs by natural selection asserts that, of the range of different individuals which make up the population of a given species, those individuals having certain characteristics contribute more offspring to the succeeding generation than those having other characteristics; and if such characteristics have an inherited basis, the composition of the population is thereby changed.
- Neanderthal Man.** *Homo neanderthalensis*, a rather recently (perhaps 50,000 years ago) extinct species of hominid from Pleistocene (mainly from early part of fourth glaciation about 100,000 years ago). Human brain size, but heavy brow ridges, low forehead, no chin prominence, did not walk fully erect.
- Neoplasm.** Tumor. Abnormal localized multiplication of some type of cell. *Malignant* if the growing cells infiltrating surrounding tissue are carried by blood or lymph to other localities in the body, there continuing their growth; otherwise *benign*.
- Nephron.** Excretory unit of vertebrate kidney, consisting of a Malpighian corpuscle and its attached urinary tubule.

Nerve. Bundle of motor and/or sensory nerve fibers with accompanying connective tissue and blood vessels, in a common sheath of connective tissue. Each nerve fiber conducts impulses independently of its fellows. See *Cranial Nerve*, *Spinal Nerve*.

Nerve Cell (Neuron, Neurone). Cell of nervous tissue which conducts the impulses by which the nervous system functions.

Nerve Ending. The structure at the peripheral end of a fiber of the peripheral nervous system, where impulses start (in a sensory fiber) or finish (in a motor fiber). May be merely the bunch of fine branching twigs by which the fiber itself ends (*free nerve ending*); or may be a distinct end organ.

Nerve Fiber. The axon of a nerve cell together with the various special membranes which may surround it.

Nerve Root. In vertebrates, each spinal nerve arises from the spinal cord by two roots—a *dorsal* (posterior in human anatomy) and a *ventral* (anterior in human anatomy) which join to form the spinal nerve as they pass through the wall of the vertebral column. The dorsal roots contain all the sensory nerve fibers, their cell bodies being in a ganglion on the course of each root. Through the ventral roots pass the motor fibers which come from cell bodies in the spinal cord.

Nervous Tissue. Nerve cells and/or their nerve fibers, together with the accessory cells which closely surround them, e.g., Schwann cells, and supporting connective tissue or glia with blood vessels.

Neural. Concerned with the nervous system.

Neurogenic. Originating in neural tissue.

Neurologia. See *Glia*.

Neurohumoral. Transmitting of effects of a nerve impulse from a nerve fiber to an end organ or across a synapse by secretion of minute amount of chemical substance from the nerve fiber. See *Cholinergic*, *Adrenergic*.

Neuron (Neurone). See *Nerve Cell*.

Neuron Theory. Theory that nervous system is made up of numerous discrete nerve cells, each originating from single cell of embryonic neural tissue, which merely make contact with each other at synapses.

Neurosis. A type of functional disorder of the nervous system.

Neutron. An electrically neutral particle of matter found in the atom.

Nicotinic Acid (Niacin, P-P Factor). A vitamin of the B group, lack of which is part of the cause of pellagra in man. Required as a vitamin by those vertebrates tested. Synthesized by many microorganisms.

Nictitating Membrane. Transparent fold of skin forming a third eyelid. When open, lies at inner (anterior) corner of eye or below lower eyelid. Occurs in some sharks and amphibia, and widespread in reptiles and birds. Well developed in a few mammals.

Norepinephrine. A compound produced by adrenergic nerves and the adrenal medulla.

Notochord. Skeletal rod (of large vacuolated cells packed within a firm sheath) lying lengthwise, between CNS and gut. Present in some stage of development of all chordates. In most vertebrates occurs complete only in embryo

(or larva), though remnants usually persist between the vertebrae which replace it in the adult.

Noxious. Harmful. Nocuous.

Nucleic Acid. Compound of pentose sugar, phosphoric acid, and nitrogen-containing base (purine or pyrimidine), often of high molecular weight, characteristic of all living things. Usually occurs as nucleoproteins. In plants and animals, occurs both in chromosomes (DNA, in which deoxyribose is the sugar) and in cytoplasm and nucleoli (RNA, in which ribose is the sugar). DNA is closely associated with, and may even be, the material of the genes. RNA is considered to play an important part in synthesis of protein.

Nucleolus. A round body within the nucleus of a cell.

Nucleoproteins. Compounds of nucleic acid and protein.

Nucleus. Body containing the chromosomes present in most cells of plants and animals.

Nucleus of Brain. Demarcated mass of nerve cell bodies, i.e., of gray matter, in vertebrate brain. Nuclei are connected by tracts of nerve fibers.

Nystagmus. Involuntary oscillatory movements of the eye.

Obesity. State of being excessively fat.

Occipital Condyle. Bony knob at back of skull articulating with first vertebra.

See *Atlas*. Double in amphibia and mammals, single in reptiles and birds.

Occiput (Occipital Region). An inexactly delimited region of the head in neighborhood of joint between skull and vertebral column.

Oculomotor Nerve. Third cranial nerve. Almost entirely motor, supplying four of the extrinsic eye muscles, inferior oblique muscle, and all rectus muscles except external, and, by nerve fibers of parasympathetic system, intrinsic eye muscles of accommodation, and pupil constriction.

Ohm. The unit of electric resistance.

Olecranon Process. Bony process on ulna of mammals extending beyond elbow joint, for attachment of muscles which straighten forelimb.

Olfactory. Of sense of smell. *O. bulb*, terminal part of cerebral hemisphere of vertebrates, from which originates *O. nerve* (first cranial nerve) running to organs of smell.

Omnivorous. Eating a diet of both plants and animals.

Oncometer. Instrument for measuring the volume of an organ, same as plethysmograph.

Oöcyte. Cell which undergoes meiosis and thereby forms ovum. *Primary oöcyte* undergoes greater part of cytoplasmic growth involved in ovum formation, and first of the two meiotic divisions. As a result of the division, it gives rise to one cell with very little cytoplasm (polar body) and one *secondary oöcyte* with massive cytoplasm. Latter undergoes second meiotic division, giving rise to another polar body and an ovum. Fertilization frequently occurs in one of the two oöcyte stages. Cf. *Spermatocyte*.

Oögenesis. Formation of ova. See *Maturation of Germ Cells*, *Oöcyte*.

Ophthalmic. See *Optic*.

Optic. Of the eye.

Optic Chiasma. Structure formed beneath vertebrate forebrain by the nerve fibers of right optic nerve crossing the left side of brain and vice versa. In most vertebrates, all the nerve fibers cross. In mammals, however, half remain on their original side, half cross.

Optic Nerve. Second cranial nerve, really part of brain wall. See *Retina*.

Orad. Toward the mouth.

Oral. Of the mouth.

Orbit. Cavity or depression in skull of vertebrates housing eyeball.

Organ. Part of an animal which forms a structural and functional unit, e.g., kidney, heart.

Organic Compound. A carbon-containing compound.

Oscilloscope. An instrument for determining time course of changes in potentials. Useful for study of bioelectric phenomena.

Osmosis. When a solution of, say, sugar in water is separated from pure water by a membrane permeable to water, but not to sugar (*semipermeable membrane*), water passes across the membrane into the sugar solution. This movement of water is osmosis.

Osmotic Pressure. The pressure exerted or capable of being exerted as a result of osmosis.

Osteoblast. Cell responsible for formation of calcified intercellular substance of bone. Cells within bone (osteocytes) are osteoblasts which have become included as the bone developed.

Osteoclast. Multinucleate cell which breaks down the calcified intercellular substance of bone. Remodelling of bone shape as a result of such breaking down constantly accompanies bone growth.

Otic. Concerning the ear. See *Auditory Organ*.

Ovarian Follicle. Sac of cells which invests developing oöcyte. Probably concerned in nourishment of growing oöcyte, and secretes estrogen. See *Graafian Follicle*.

Ovary. Organ which produces ova. In vertebrates, it also produces sex hormones. See *Estrogen*, *Progesterone*.

Oviduct. Tube carrying ova from ovary to uterus.

Ovulation. Bursting of ripe egg from ovarian follicle. In vertebrates, the egg (actually a secondary oöcyte) is discharged onto surface of ovary and thence passes into oviduct. See *Menstrual Cycle*.

Ovum. Unfertilized egg cell.

Oxidase. Enzyme (a kind of dehydrogenase, q.v.) which catalyzes oxidation of a substrate by removal of hydrogen which combines with molecular oxygen

Oxygen Debt. Oxygen consumed, in excess of normal amounts, when an organism or part of an organism has been respiring with inadequate oxygen supply; e.g., after hard muscular work oxygen consumption of man remains above normal for some time, until the debt has been repaid.

Oxyhemoglobin. The compound formed by the union of hemoglobin with oxygen.

Oxytocin. Substance extracted from posterior lobe of pituitary which produces strong contraction of uterine muscle.

Pacemaker. Region of vertebrate heart where contraction at each beat is started—the sinus venosus (a contractile chamber of heart) or its homologue in mammals and birds, the sinoauricular node (a small group of cells in wall of auricle).

Palate. Roof of mouth.

Pancreas. Gland situated in mesentery near duodenum, into which it discharges through pancreatic duct an alkaline mixture of digestive enzymes (trypsinogen, lipase, amylase, maltase, etc.). Also contains groups of cells (islets of Langerhans) secreting the hormone, insulin.

Panthothenic Acid. Vitamin of B group.

Papilla. Any minute nipple-shaped elevation.

Parasympathetic System. Craniosacral division of autonomic nervous system.
Cf. *Sympathetic System*.

Parenchyma. The specific tissue of an organ, as opposed to the blood vessels, connective tissue, etc.

Parasthesia. An abnormal sensation such as burning or tingling, "pins-and-needles" sensation.

Parietal. (1) Of coelomic lining (peritoneum or pleura), that covering inside of body wall, as opposed to *visceral* part covering organs within coelom.

(2) *P. bones*, pair of membrane bones which in most vertebrates covers large part of upper surface of brain, behind frontal bones. (3) *P. organ*, see *Pineal Apparatus*.

Paroxysmal. Recurring abruptly.

Parturition. Childbirth.

Patella. Kneecap. A bone (sesamoid bone, q.v.) over the front of the knee-joint tendon of muscles which straightens the leg. It is present in most mammals, and in some birds and reptiles.

Pathogen. Microorganism or material which causes disease.

Pelvic Girdle. See *Hip Girdle*.

Pelvis. (1) The pelvic girdle. (2) The lower part of the abdomen surrounded by the pelvic girdle. (3) *P. of kidney*, funnel-shaped expansion of ureter as it joins the concave side of kidney.

Penis. Organ associated with duct from testis, used to introduce sperm from male into female.

Pentadactyl Limb. The kind of limb found in the four classes of vertebrates (amphibia, reptiles, birds, and mammals) which collectively are called the tetrapods. Evolved as an adaptation to life on land, and therefore not found in fishes or other primitively aquatic vertebrates. The limb is in three parts—upper arm or thigh, forearm or shank, hand or foot. The latter bears five terminal fingers or toes (digits), hence the name pentadactyl. The first part contains one long bone (humerus in arm, femur in leg), the second part, two long, more or less parallel, bones (radius and ulna in arm, tibia and fibula in leg), the third part, many small bones in a fairly uniform pattern (carpals, metacarpals, and phalanges successively in arm; tarsals, metatarsals, and phalanges in leg). Many modifications of this fundamental pattern occur, through loss or fusion of elements, especially in the terminal parts.

Pentose. A simple sugar having the general formula $C_5H_{10}O_5$.

Pepsin. Enzyme (proteinase, q.v.) splitting proteins into peptones in acid solution. Secreted in stomach, along with hydrochloric acid.

Peptidase (Exopeptidase). An enzyme splitting peptones or peptides by attacking terminal peptide linkages, splitting off amino acids.

Peptide. Compound formed of two or (polypeptide) more amino acids, by amino (NH_2) group of one joining with carboxyl ($COOH$) group of the next, forming *peptide link* ($-NH-CO-$) with elimination of water.

Peptone. Product of protein splitting; more complex than peptides, but not sharply demarcated from them.

Perfusion. Artificial passage of fluid through blood vessels of an organ or animal. Fluid may be fixative; saline to wash out blood; or may approximate blood in composition in order to keep organ alive after isolation from animal.

Pericardial Cavity (Pericardial Sac). Cavity within which heart lies.

Pericardium. The membranous sac which contains the heart.

Perineum. Region of body wall between anus and urogenital openings.

Periosteum. Layer of connective tissue tightly investing bones, to which muscles and tendons are attached. Contains active or (in adult) potential osteoblasts; in embryo, and in adult after fractures, important in formation of bone.

Peripheral Nervous System. The nervous system exclusive of brain and spinal cord.

Peristalsis. The rings of contraction that move along tubular structures such as the intestine, ureters, oviducts, etc.

Peritoneal Cavity. Abdominal cavity. Coelomic cavity of mammals posterior to diaphragm, containing liver, spleen, most of gut, and other viscera which almost completely fill it.

Peritoneum. The membrane which lines the abdominal walls and envelops the abdominal viscera.

Peritonitis. Inflammation of the peritoneum.

Permeability. Of a membrane, extent to which molecules of a given kind can pass through it.

Pes. Foot of hind leg of tetrapod vertebrate. Consists of tarsus, metatarsus, and digits. See *Pendactyl Limb*. Cf. *Manus*.

pH. A quantitative expression for acidity or alkalinity of a solution, i.e., concentration of hydrogen or hydroxyl ions. Scale ranges from 0 to 14, 7 being neutral, less than 7 acid, more than 7 alkaline. Concentration of hydrogen or hydroxyl ions increases or decreases ten times for each unit of change in pH.

Phagocyte. A cell which engulfs into its cytoplasm particles from its surroundings, by a process of flowing all round them called *phagocytosis*. Phagocytes are an important defence mechanism against invading bacteria. In man and other mammals, polymorphs and macrophages are phagocytic.

Phalanges. Bones of digit (finger or toe). Each finger has one to five phalanges joined end-to-end in a row, the proximal of each row being jointed to a metacarpal bone.

Pharynx. Part of gut between mouth and esophagus, into which glottis opens.

Partly divided by soft palate into upper (nasal) section and lower (oral) section.

Phenotype. The sum of the characteristics manifested by an organism, as contrasted with the set of genes possessed by it (genotype, q.v.).

Phosphagen. Phosphate of creatine, or of arginine (an amino acid). Reversible splitting off of phosphate from phosphagen plays important part in providing readily available store of energy-rich phosphate for ATP (q.v.) in muscular contraction.

Phosphatases. Enzymes splitting phosphate from its organic compounds.

Phospholipid (*Phospholipin*, *Phospholipoid*, *Phosphatide*). Lipid containing phosphoric acid and nitrogenous base, e.g., lecithin.

Phosphorylation. Combination (e.g., of sugar) with phosphoric acid.

Photoreceptor. Receptor detecting light, e.g., vertebrate eye.

Photosynthesis. Synthesis by green plants of glucose from water and carbon dioxide using energy absorbed from sunlight.

Phylum. One of the major kinds of group used in classifying animals, e.g., Phylum Chordata. See *Classification*.

Physiology. Study of the processes which occur in living organisms.

Pia Arachnoid. Delicate membranes ensheathing central nervous system—*Pia mater* immediately covering central nervous system, containing many blood vessels; *arachnoid* outside that, in contact with *dura mater* and separated from *pia* by spaces filled with cerebrospinal fluid.

Piloerection. Erection of hairs of the skin.

Pineal Apparatus. Primitively consists of two outgrowths of roof of forebrain lying within skull, one behind the other (though may represent right and left of a pair). Anterior is *parietal organ* which forms an eye-like structure (*pineal eye*) in some lizards and *Sphenodon*, a vestigial eye in lamprey (*Cyclostomata*), and is reduced or absent in other vertebrates. Posterior forms a second, functional eye-like structure in lamprey, and the glandular *p'neal body* or *epiphysis* of other vertebrates.

Pineal Body (*Epiphysis*). See *Pineal Apparatus*. Its function is unknown, but often is assumed to secrete a hormone.

Pinna. See *Ear*, *Outer*.

Pithecanthropus. Java ape-man. Lower Pleistocene. Brain of human type, but small; walked erect; ape-like in heavy brow ridges and absence of chin prominence.

Pitressin. Extract of posterior lobe of pituitary, causing, when injected, constriction of capillaries and arterioles (which raises arterial pressure) and diminished urine formation. Also called *vasopressin*. See *Antidiuretic Hormone*.

Pituitary Body (*Pituitary Gland*, *Hypophysis Cerebri*). Endocrine gland beneath floor of brain, within skull, of vertebrates. Two main regions, *anterior lobe* (or *anterior pituitary*) and *posterior lobe* (or *posterior pituitary*), separated by a cleft.

Pituitrin. Extract of posterior lobe of pituitary having activity of both oxytocin and pitressin.

Placenta. Organ consisting of embryonic and maternal tissues in close union, by

- which embryo of viviparous animal is nourished. In placental mammals, the embryonic tissue concerned is the chorion, with blood vessels supplied via allantois or occasionally via yolk sac.
- Placentation.** Type of arrangement of placenta.
- Plantigrade.** Walking, as does man, on ventral surface of whole foot, i.e., of metacarpus or metatarsus and of digits.
- Plasma.** The liquid portion of the blood which remains when coagulation is prevented. Cf. *Serum*.
- Plasma Membrane (Cell Membrane).** Extremely thin membrane of fat and protein covering surface of all cells (or protoplast in plants). Responsible for restricted penetration of many substances into interior of cell (see *Permeability*).
- Plasma Proteins.** Dissolved proteins of blood plasma. Among plasma proteins are antibodies and blood-clotting substances. See *Albumen*, *Globulins*, *Fibrinogen*.
- Plasmolysis.** Shrinkage of a cell, produced by withdrawal of water from the cell into a hypertonic solution.
- Platelet.** See *Blood platelets*.
- Plethysmograph.** Instrument for measuring variations in volume of an organ; same as oncometer.
- Pleura.** The membrane lining the chest cavity and covering the lungs.
- Pleural Cavity (Pleural Sac).** Coelomic space surrounding lung in mammal, separated from rest of perivisceral coelom by diaphragm. There is a pair of pleural sacs separated from each other by mediastinum and pericardial sac. Actual space of sac is normally a thin layer of fluid between pleura of lungs and body wall, which are substantially in contact.
- Pleurisy.** Inflammation of the pleura.
- Pneumotaxic.** Regulating rhythmicity of breathing.
- Poikilothermic.** Having a variable body temperature; cold-blooded.
- Polar Body.** Minute cell produced during development of oöcyte containing one of the nuclei derived from first or second division of meiosis, but practically no cytoplasm.
- Polarization.** Unequal distribution of positive and negative electrical charges so that a difference in potential develops, e.g., polarization of the membrane of a nerve fiber.
- Polymorph (Polymorphonuclear Leucocyte, Granulocyte).** Kind of white blood cell, 7-9 microns diameter with darkly staining nucleus constricted into a number of lobes. Cytoplasm usually contains conspicuous granulations.
- Polypeptide.** A simple protein consisting of a relatively small number of amino acid units.
- Polysaccharide.** Complex carbohydrates having the general formula $(C_5H_{10}O_5)_n$; includes starch and cellulose.
- Portal Vein.** Vein carrying blood from one capillary network to another. See *Hepatic Portal System*.
- Posterior.** Toward the back; in man, dorsal.
- Posterior Root.** Nerve root, synonymous with dorsal root.

Postganglionic. Beyond the ganglion in a peripheral nerve pathway; fibers in the autonomic system which lead from the ganglion to the effector cells.

Preganglionic. Before the ganglion in a peripheral nerve pathway; fibers of the autonomic system which terminate at synapses in ganglia.

Premaxilla. Dermal bone forming front part of upper jaw and bearing incisor teeth.

Premolars. Those crushing teeth which (unlike molars) have predecessors in the deciduous set of teeth. They have usually more than one root and a pattern of ridges and projections on biting surface. See *Dental Formula*.

Pressor. Tending to cause a rise in arterial blood pressure.

Pressoreceptor. Receptors in the carotid sinuses and aortic arch which are stimulated by a rise in arterial blood pressure.

Primate. A member of the Primates, an order of placental mammals including man, apes, and monkeys.

Proenzyme. The precursor of an enzyme.

Progesterone. Hormone (a steroid) secreted by corpus luteum of mammalian ovary, responsible for preparing reproductive organs for pregnancy, as in luteal phase of estrous cycle, and for maintaining uterus in special state for nourishment and protection of embryo during pregnancy, when it is also produced by placenta.

Prolactin. See *Lactogenic Hormone*.

Pronation. Position, or rotation towards the position, of forelimb such that forefoot (hand) is twisted through 90 degrees relative to elbow, the radius and ulna being crossed. Men and other primates can untwist the forearm (*supination*).

Prophase. Initial stage of mitosis or meiosis during which chromosomes appear within the nucleus, and in meiosis undergo pairing.

Proprioceptor. Receptors which are concerned with giving information concerning movements and position of the parts of the body.

Prostate Gland. Gland of male reproductive system of mammals which contributes substances to semen. Its size and secretory powers are controlled by androgens.

Protease. See *Proteolytic Enzyme*.

Protein. Nitrogenous compounds formed by the union of many amino acids by peptide linkages.

Proteinase (Endopeptidase). Proteolytic enzyme splitting whole protein molecules, mainly into polypeptides, by attacking peptide linkages between certain specific amino acids wherever these occur. See *Trypsin*, *Pepsin*.

Proteolytic Enzyme (Protease). Any enzyme taking part in breaking down of proteins, e.g., proteinase or peptidase. A system of several proteases is necessary to break proteins down to constituent amino acids.

Prothrombin. See *Blood Clotting*.

Proton. Unit of positive electricity. The elementary particle carrying the positive charge (hydrogen nucleus).

Protoplasm. The form of matter in which life is manifested.

Proximal. Situated towards point of attachment. Cf. *Distal*.

Ptyalin. An amylase present in saliva.

Puberty. The period in life at which the reproductive organs become functionally operative.

Pubic Symphysis. Joint or fusion formed midventrally between pubic bones of two halves of pelvic girdle. See *Symphysis*.

Pubis. Ventral, forward-projecting part of hip girdle.

Pulmonary. Of the lung.

Pulp Cavity. Internal cavity of tooth or denticle, open by usually a narrow channel to tissues in which tooth is embedded, containing connective tissue, nerves, and blood vessels, with odontoblasts lining the dentine wall of the cavity.

Pulse. Wave of raised pressure which passes rapidly from heart outwards along all the arteries each time the ventricle pumps blood into the aorta. The increased pressure dilates the arteries, and this can be felt.

Purpura. A condition characterized by the appearance of small purple patches in the skin and mucous membranes.

Pylorus. Junction between stomach and duodenum. Has a sphincter muscle within a fold of mucous membrane which can close off the junction.

Pyridoxine (Vitamin B6). Vitamin of B group, forming a coenzyme, required by variety of organisms, e.g., some of the yeasts, bacteria, insects, birds, and mammals; not certainly by man.

Quadruped. See *Tetrapoda*.

Radius. The anterior of the two bones (other is ulna) of forearm of tetrapod vertebrate forelimb. Articulates with side of hand (forefoot) on which thumb is located.

Reaction Time. See *Latent Period*.

Receptor (Sense Organ). That part of an animal which, in co-operation with the nervous system, detects what goes on (i.e., receives stimuli from) outside or inside the animal. Of different kinds, each especially sensitive to a specific sort of stimulus, such as temperature, light, or muscular movement.

Recessive. Converse of dominant (q.v.). A recessive gene has no effect on phenotype unless homozygous.

Rectum. Terminal part of intestine, opening to exterior by anus.

Red Blood Cell or Corpuscles (Erythrocytes). Blood cells containing hemoglobin. Important in carrying oxygen. Each is a circular biconcave disc about 8 microns in diameter after fixation, and there are roughly five million per milliliter of blood.

Reflex. Very simple form of behavior in which a certain kind of stimulus almost invariably evokes one specific kind of simple response. E.g., a pin stuck in one's foot evokes an immediate withdrawal. The consistency and immediacy of response depends on an inborn nervous pathway (i.e., one which is independent of experience), along which the impulses travel. It involves the central nervous system.

Refraction. The bending of light rays in passing obliquely from one medium to another of different density.

Rennin. Enzyme secreted in the stomach of young mammals which clots milk (converting soluble protein caseinogen into casein which forms insoluble calcium-casein compound).

Respiration. (1) Breathing, e.g., pumping air in and out of lungs. (2) Taking oxygen from the environment and giving off carbon dioxide.

Respiratory Enzyme. Enzyme which catalyzes oxidation-reduction reactions. See *Dehydrogenase, Oxidase*.

Respiratory Pigment. Substance which combines reversibly with oxygen, thus acting as a carrier or store of it. E.g., hemoglobin of human blood becomes loaded with oxygen in the lungs where it comes into equilibrium with air; and it gives up this oxygen when it comes into contact with tissues having a low oxygen pressure.

Respiratory Quotient (RQ). Ratio of the volume of carbon dioxide expired to the volume of oxygen consumed during the same time.

Response. Change in an organism or part of it produced by a stimulus. See *Irritability*.

Resting Potential. The potential difference between the outside and inside of a nerve fiber, a muscle fiber, or gland cell. The outside is positive compared with the inside.

Reticulo-Endothelial System. Those phagocytic macrophages in contact with blood (in bone marrow, spleen, liver) or lymph (in lymph nodes); they free these fluids from foreign particles, e.g., bacteria. See *Macrophages*.

Retina. Layer lining interior of eye, except at front in region of ciliary body); it is sensitive to light. It has an outer pigmented layer, next to the choroid, and an inner transparent nervous layer next to cavity of eyeball. The nervous layer contains light-sensitive rods and/or cones in contact with pigmented layer, and nerve fibers, intermediary nerve cells, blood vessels, and glia interposed between incoming light and rods and cones.

RH Factor (Rhesus Factor). Substance (an antigen; there are actually several, closely related) occurring in blood corpuscles of a high proportion of human beings (85 per cent in Great Britain and U.S.A.).

Riboflavin (Vitamin B₂). Vitamin of B group. Forms part of various enzymes concerned in cellular oxidation, widely distributed in living organisms. Liver, muscle, yeast are important sources. Required as vitamin by those vertebrates (including man) and insects tested, and by some bacteria. Synthesized by many bacteria, including those present in human intestine.

Ringer's Solution. Solution containing sodium, potassium, and calcium chlorides (and sometimes other salts), these being main salts in fluid which normally bathe cells. Used in physiological experiments for temporarily maintaining cells or organs alive in vitro.

RNA. Ribose nucleic acid. See *Nucleic Acid*.

Rod. Kind of light-sensitive nerve cell present in retina. Rods do not discriminate fine detail nor probably color differences, but they are sensitive to very dim light, which cones are not.

RQ. See *Respiratory Quotient*.

Saccule. See *Ear, Inner*.

Sacral Vertebra. Vertebra of tetrapods which articulates by means of rudimentary ribs with ilia of hip girdle.

Sacrum. Group of sacral vertebrae fused together, the ilia of the hip girdle being united to some or all of them. See *Hip Girdle*.

Sagittal. Running in an anteroposterior direction. The midsagittal plane divides the body into right and left halves.

Saliva. Fluid containing mucus and ptyalin secreted from salivary glands into mouth.

Schwann Cell. Kind of cell which ensheaths nerve fibers of vertebrate peripheral nervous system. In a myelinated fiber, one cell occurs between every pair of adjacent nodes.

Sclerosis. Hardening.

Sclerotic. Fibrous or cartilaginous firm outer coat of eyeball continuous with cornea in front of eye.

Scrotum. Pouch of skin which contains testes.

Sebaceous Gland. Skin gland of mammals nearly always opening into a hair follicle, secreting fatty substance (sebum). Formed from epidermis, but projects deep into dermis.

Secondary Sexual Character. A characteristic of animals which differs between the two sexes, but excluding the gonads, and the ducts with their associated glands, which convey the gametes.

Secretin. Hormone which stimulates secretion of digestive juices by pancreas, and of bile by liver. Produced in epithelium of wall of duodenum and jejunum under stimulus of acid products of digestion coming through pylorus from stomach. A peptide.

Secretion. (1) The passage of material elaborated by cell from the inside to the outside of its plasma membrane; the material (itself called a secretion) having a special function in the organism. Secretion is probably an activity of most cells, but is specialized in gland cells. Usually takes place by extrusion of material, but may involve pinching off part (apocrine secretion, e.g., mammary gland) or even destruction of whole cell (holocrine secretion, e.g., sebaceous gland). (2) Secretion, when used in contrast to simple diffusion, means that the cell does work in passing the substances through its plasma membrane against the forces of diffusion.

Segmentation. (1) *Metameric segmentation. Metamerism.* Repetition of a pattern of elements belonging to each of the main organ systems of the body, along the anteroposterior axis of the body, or a comparable repetition along the axis of an appendage. Vertebrates show segmentation most clearly in embryonic development, but it is almost confined to parts of the muscular, skeletal, and nervous systems. (2) In embryology, a synonym for cleavage (q.v.).

Segregation. Separation into different gametes, and thence into different offspring, of the two members of any pair of allelomorphs possessed by an in-

dividual; the two allelomorphs having previously been brought together in the individual, one from each of its parents, and having in no way blended or altered each other while associated together in the individual. Mendel's first law asserts that allelomorphs segregate.

Semen. Product of male reproductive organs, consisting of sperm together with secretions of various accessory glands, e.g., of prostate gland in mammals.

Semicircular Canals. Semicircular tubes, projecting from, and joined at both ends to, the inner ear of vertebrates. There are three on each side, occupying the three planes of space, two vertical at right angles to each other, one horizontal.

Seminal Vesicle. Organ which stores sperm in the male.

Seminiferous Tubules. Coiled tubes made of germinal epithelium. During sexual activity, all stages of spermatogenesis occur in time, up to almost mature sperm. Supposedly nutritive Sertoli cells, to which developing spermatids are attached, are also present. Correspond to ovarian follicles of ovary.

Semipermeable. Permitting the passage of some molecules in solution, while not permitting the passage of others.

Sense Organ. See *Receptor*.

Sensory. Concerned with receptors (q.v.). *S. nerve.* Peripheral nerve consisting of nerve fibers of sensory nerve cells. *S. nerve fiber.* Nerve fiber of a sensory nerve cell. *S. nerve cell* (*S. neuron*). Nerve cell whose fibers connect with receptor, transmitting impulses started by receptor to central nervous system. The cell body of such a nerve cell is attached to its nerve fiber at a point along its course situated in dorsal root ganglion. *S. root.* Nerve root containing the sensory nerve fibers.

Septum. Partition or wall.

Serous Membrane. Mesothelium and underlying connective tissue lining celomic spaces (pericardial, pleural, peritoneal cavities).

Sertoli Cells. See *Seminiferous Tubules*.

Serum. The liquid part of the blood which separates from the clot.

Sesamoid Bone. Bone developed within a tendon, particularly where tendon works over ridge of underlying bone, e.g., patella (kneecap).

Sex Chromosomes. So called because they are concerned with determining the sex of the individual. See X-Chromosome, Y-Chromosome.

Sex Determination. See *Sex Chromosomes*.

Sex Linkage. Of a gene or character, having special distribution with reference to sex as a result of (in the case of a gene) being carried on the X-chromosome (q.v) or (in the case of a character) controlled by a gene so carried.

Sexual Reproduction. Reproduction involving fusion of gametes, one of which is derived from the male and one from the female.

Shoulder Girdle (Pectoral Girdle). Skeletal support in body wall for attachment of front limbs. Consists primitively of a curved bar of cartilage or bone on each side of the body, the two often fusing ventrally, forming a hoop, incomplete dorsally, transverse to long axis. Each bar bears a joint with limb. See *Glenoid Cavity*. Region dorsal to joint is *scapula*, region ventral is *coracoid*. Extradermal bones, notably *clavicle*, usually occur on ventral

side. Scapula forms no joint with, or bony attachment to, vertebral column or ribs. Coracoid and clavicle are joined midventrally to breast bone (sternum).

Siblings. Offspring of same parents.

Sinus. A cavity or recess or hollow space.

Sinusoids. Small blood vessels which take the place of capillaries in some organs, notably liver and bone marrow. Differ from capillaries in diameter (often much wider) and absence of regular endothelium. Macrophages (q.v.) lie in walls.

Sinus Venosus. Chamber of vertebrate heart, lying between veins and auricles; thin walled; absent in adult birds and mammals. See *Pacemaker*.

Skeletal Muscle. See *Striated Muscle*.

Smooth (Plain, Involuntary) Muscle. Contractile tissue of vertebrates, consisting of numbers of individual, elongated spindle-shaped cells, with no transverse striations, bound together by connective tissue fibers. Found mainly in sheets surrounding hollow organs, e.g., blood vessels, gut. Controlled by autonomic nervous system. Cf. *Striated Muscle*.

Solute. A substance in solution; a solution consists of solvent and solute.

Solvent. A liquid that is capable of dissolving a substance.

Somatic. Pertaining to the body, especially to the portion other than the viscera.

Somatic Cells (Soma). The cells of an organism, other than the germ cells.

S. tissues. Tissues other than those of viscera or blood vessels; tissues which surround body cavity (q.v.). *S. motor nerves* supply skeletal muscle; *S. sensory nerves* supply receptors of somatic tissues.

Somitic Mesoderm. Mesoderm on dorsal side of vertebrate embryo, flanking the notochord in two longitudinal strips, each of which as development proceeds becomes segmented into a series of blocks, the *somites*. (In front of the ears, however, there is usually no segmentation into somites.) From each somite is derived a myotome (q.v.) innervated by one ventral nerve root (so that nerves are also segmentally arranged), and mesenchyme which forms connective tissue and the vertebral column.

Spasticity. Marked hypertonus of muscles.

Species. The smallest unit of classification commonly used, i.e., the group whose members have the greatest mutual resemblance. For the great majority of animals, a species is roughly a group of individuals who are able to breed among themselves, but not able to breed with organisms of other groups. Consequently, the members of a species form a reproductively isolated group, whose genes do not combine with those of outsiders, but are able to recombine continually by sexual reproduction within the group. For naming of species, see *Binomial Nomenclature*.

Sperm. See *Spermatozoon*.

Spermatid. Animal cell resulting from the (second) meiotic division of a secondary spermatocyte (q.v.). At first, a cell of normal shape, it undergoes extensive cytoplasmic changes and condensation of nucleus which convert it into a spermatozoon.

Spermatocyte. Cell which undergoes meiosis, and thereby forms spermatids (q.v.). Primary spermatocyte undergoes first of the two meiotic divisions. As a result, it gives rise to two *secondary spermatocytes*. The latter undergo the second meiotic division, each forming two spermatids (q.v.). One primary spermatocyte thus produces four spermatozoa. Cf. *Oöcyte*.

Spermatogenesis. Formation of sperm. See *Maturation of Germ Cells. Spermatocyte*.

Spermatogonium. Cell of animal gonad which undergoes repeated mitosis and eventually gives origin to spermatocytes (q.v.).

Spermatozoon. Small, motile male gamete.

Sphincter. A ring-like muscle which closes a natural orifice.

Sphygmomanometer. Instrument for indirect measurement of blood pressure.

Spinal column. See *Vertebral Column*.

Spinal Cord. That part of the vertebrate central nervous system which lies within the backbone. Contains numerous nerve cells and bundles of nerve fibers, particularly those connecting all levels of the spinal cord with the brain. Pairs of peripheral nerves, one nerve on each side per segment, leave the spinal cord to be distributed to the body. See *Nerve Root*.

Spinal Nerve. Peripheral nerve arising from spinal cord. One on each side in each segment. See *Nerve Root*. Cf. *Cranial Nerve*.

Spleen. Mass of lymphoid tissue in mesentery of stomach or intestine interposed in blood circulation. An important source of lymphocytes, and an important part of reticulo-endothelial system. Produces red blood cells. Acts as a store of red blood cells and, in emergency, contraction of the smooth muscle in the spleen squeezes them into blood stream.

Stapes. One of the three mammalian ear ossicles. Stirrup shaped.

Stenosis. Narrowing or stricture of a duct or canal.

Stereognosis. Faculty of recognizing the shape and nature of objects by the sense of touch.

Sternum. Breast bone. Bone in the middle of the anterior side of the chest, to which the anterior ends of most of the ribs are attached. At its superior end it is attached to shoulder girdle.

Steroid. A group name for compounds having a characteristic four-ring system known as a cyclopentophenanthrene ring.

Sterols. Compounds with the general chemical ring structure of a steroid, but with certain specific features of structure, including a long side chain and an alcohol group. Sterols occur universally in plants and animals, e.g., cholesterol, ergosterol.

Stimulus. Any change in the environment of an organism or of part of it which is sufficient to elicit a response.

Stomach. Enlargement of the anterior region of the gut. Follows esophagus. Has muscular walls which churn food, and lining cells which secrete pepsin and hydrochloric acid.

Striated Muscle (Striped, Skeletal, Voluntary Muscle). Contractile tissue consisting of large elongated cells (muscle fibers) with many nuclei, the cytoplasm of which bears conspicuous striations at right angles to long axis.

Cytoplasm contains numerous longitudinal fibrils, each having alternating bands of different composition; the cross striations of the whole muscle fiber are the result of similar bands of the fibrils lying side by side. Cf. *Cardiac Muscle*, *Smooth Muscle*.

Striped Muscle. See *Striated Muscle*.

Subcutaneous. Immediately below dermis of vertebrate skin. *S. tissue* is usually loose connective tissue, which may contain much fat.

Subliminal. Below threshold.

Submaximal. Below the maximum, usually used in reference to stimuli.

Succus Entericus. Digestive juice secreted by walls of small intestine. Contains numerous enzymes, e.g., erepsin, sucrase, lactase, and enterokinase.

Sucrase. Enzyme which acts on sucrose, splitting it (by hydrolysis) into glucose and fructose; also called *invertase*.

Sucrose. Cane sugar. A disaccharide (with twelve carbon atoms) widespread in plants, but not in animals. Not found in mammalian body, except in food in gut. It is produced by dehydration synthesis of one molecule of glucose and one of fructose.

Summation. Accumulative effects of impulses at synapses or of stimuli applied to nerve or muscle fibers.

Supramaximal. Greater than the maximal; used to describe electrical stimuli of greater strength than that needed to produce a maximal response.

Suprarenal Gland. See *Adrenal Gland*.

Survival Value. The nature or degree of the effectiveness of a given characteristic in promoting the organism's ability to contribute offspring to the future population. See *Natural Selection*.

Suture. (1) Anatomical. Junction between the irregular interlocking edges of certain contiguous skull bones. In man, sutures slowly become obliterated during life by fusion of adjacent bones. (2) Surgical. To sew a wound together.

Sweat Glands. Skin glands secreting a dilute (hypotonic) solution of the salts and other solutes present in blood. Function, cooling by evaporation. Production of sweat is under control of cholinergic fibers in the sympathetic nervous system. Formed from epidermis, but project deep into dermis.

Sympathetic Ganglion. See *Autonomic Nervous System*.

Sympathetic System. Part of autonomic nervous system (q.v.) sometimes called *orthosympathetic*. Equivalent to thoraco-lumbar part. Cf. *Parasympathetic System*.

Sympathin. Substance which enters circulation when adrenergic nerves are stimulated, now considered to be epinephrine or nor-epinephrine.

Sympathomimetic. Acting like epinephrine. Adrenomimetic.

Symphysis. Type of joint allowing only slight movement, in which the surfaces of the two articulating bones, both covered with a layer of smooth cartilage, are closely tied together by collagen fibers, e.g., pubic symphysis and joints between centra of vertebral column.

Synapse. Junction between two neurons at which excitation or inhibition is mediated.

Syncytium. Tissue in which cells are so intimately joined as to constitute a single mass of protoplasm.

Syndrome. A set of symptoms which occur together in a given disease.

Synergism. (1) Combined activity of agencies, e.g., drugs, hormones, which separately influence a certain process in the same direction such that an effect is produced greater than sum of effects of each agency acting alone. (2) Sometimes used for combined activity such that effect is either sum of the separate effects (summation), or greater than the sum of the separate effects (potentiation), it does not matter which; i.e., the agencies are not antagonistic to each other.

Synovial Membrane. Membrane of connective tissue lined with flattened cells (mesothelium) forming a bag enclosing a freely movable joint, e.g., elbow joint, being attached to the bone at either side of the joint. The bag is filled with a viscous fluid (*synovial fluid*) containing mucoprotein, lubricating the smooth cartilage surfaces which make the contact between the two bones.

Systemic. Generally distributed throughout an organism.

Systole. Period of the cardiac cycle during which the muscle is in a state of contraction.

Tactile. Of touch. *T. corpuscle.* Receptor end organ of touch.

Tarsal Bones (Tarsals). Bones of the proximal part of the hindfoot (roughly the ankle) in tetrapod vertebrates. Cf. *Carpal Bones* of forefoot. Seven in man, one of them (calcaneum) forming the heel. Articulate on proximal side with tibia and fibula, on distal side with metatarsals.

Taste Bud. Receptor end organ for taste.

Taxonomy. The science which deals with classification of plants and animals.

Telophase. Terminal stage of mitosis or meiosis during which nuclei revert to resting stage.

Tendon. Cord or band of connective tissue attaching muscle, usually to a bone.

Testis. Organ of animals which produces sperm and hormones. See *Androgen*.

Testosterone. An androgen (q.v.), probably the principal one produced within male vertebrates. A steroid.

Tetany. A syndrome characterized by flexion of the wrist and ankle joints (carpopedal spasm), muscle twitching, cramps, and sometimes convulsions.

Tetrapoda. A grouping of vertebrate classes sometimes used in classification. Includes amphibians, reptiles, birds, and mammals (i.e., all the essentially land-living vertebrate classes). All characterized by two pairs of pentadactyl limbs (q.v.). A quadruped.

Thalamus. Part of the forebrain. It is a major sensory coordinating region.

Theca. A case or sheath.

Thiamin (Aneurin) (Vitamin B₁). Its phosphate is a co-enzyme (cocarboxylase). Very widely distributed in living organisms.

Thoracic Duct. Main lymph vessel, receiving lymph from trunk (including lacteals) and legs, running up the thorax close to the vertebral column on the left, and discharging into venous system at the angle formed by the junction of the left internal jugular and subclavian veins.

Thorax. In terrestrial vertebrates, region of the body containing heart and lungs (chest). Only in mammals is it clearly marked off from the abdomen by the diaphragm.

Threshold. That intensity of stimulus below which there is no apparent response by a given irritable tissue; however, stimuli below threshold can summate to elicit a response.

Thrombin. See *Blood Clotting*.

Thrombocyte. See *Blood Platelets*.

Thrombosis. The formation of a thrombus or clot.

Thrombus. A clot formed in a blood vessel and adhering to the wall of the vessel. Cf. *Embolus*.

Thymus. Lymphoid organ which lies in chest (mediastinum) just above the heart. Reaches maximum size at puberty, and thereafter slowly atrophies.

No clearly demonstrated function other than the production of lymphocytes.

Thyroglobulin. The form in which thyroid secretion is stored in thyroid gland.

Thyroid Gland. An endocrine gland. Unpaired organ in the neck region.

Secretes an iodine-containing hormone. See *Thyroxin*, *Thyroglobulin*.

Thyrotropic (Thyrotrophic) Hormone. Hormone secreted by anterior lobe of pituitary. Stimulates secretory activity of thyroid gland.

Thyroxin. An iodine-containing amino acid, probably the thyroid hormone.

Tibia. Shin bone. The anterior of the two long bones (other is fibula) of the shank (below the knee) of the hind limb of tetrapod vertebrates.

Tissue. A region consisting mainly of cells of the same sort (performing the same function) associated in large numbers. Four main types are epithelial, connective, neural, and muscular.

Titer. Measure or amount.

Tonsil. Mass of lymphoid tissue in pharynx. Lies close underneath mucous membrane, deep crevices of which may communicate with interior of tonsil. Man has a pair of palatine tonsils (at junction of mouth and pharynx) and a single pharyngeal tonsil ("adenoids" at back of nose).

Tonus (Tone). Continuous, but usually moderate, physiological activity of a tissue or organ; e.g., striated muscle, as a result of continuous nervous stimulation, is normally in a state of moderate contraction (tonus), by which the posture is maintained.

Trachea. The "windpipe" which leads from the throat, starting at the glottis, through the neck to the point where it bifurcates into two bronchi.

Tract. Spatially delimited bundle of nerve fibers, usually all having similar connections, in central nervous system. Tracts connect nuclei with each other and with peripheral nervous system.

Transverse Process. Lateral projection, one on each side, of the neural arch of vertebra with which head of rib articulates.

Tricuspid Valve. Valve between right auricle and right ventricle of mammalian heart. It consists of three membranous flaps, or cusps.

Trigeminal Nerve. Fifth cranial nerve. In mammals, mainly sensory, innervating teeth and skin of face.

Triploblastic. Having the body made up of three layers (ectoderm, mesoderm,

endoderm). As in all Metazoa except coelenterates, which are diploblastic. See *Germ Layer*.

Trochanter. A prominence on the femur of vertebrates to which muscles are attached. There are three trochanters on each femur in mammals. The largest one in man is the conspicuous bony prominence at the hip joint.

Trochlear Nerve. Fourth cranial nerve. Almost entirely motor, supplying eye muscle (superior oblique).

Trophoblast. Embryonic epithelium which encloses all embryonic structures of placental mammals, forming outer layer of chorion (q.v.), and establishing close contact with maternal tissues. Forms embryonic side of placenta (q.v.).

Trypsin. Enzyme splitting proteins at certain specific peptide links, in alkaline solution, forming mainly polypeptides. Secreted by pancreas.

Trypsinogen. Almost inactive form in which trypsin is secreted by pancreas. Converted to trypsin by enterokinase or by trypsin already formed.

Tympanic Cavity. See *Ear, Middle*.

Tympanic Membrane. Ear drum. Double layer of epidermis with connective tissue between. See *Ear, Middle* and *Outer*.

Ulna. The posterior of the two bones (other is radius) of forearm. Articulates with side of hand opposite to that on which thumb is located.

Umbilical Cord. Stalk projecting from ventral surface of embryo of placental mammal and connecting it with placenta.

Urea. Main excreted product of protein breakdown in mammals. A nitrogen-containing organic compound, $\text{CO}(\text{NH}_2)_2$, readily soluble in water.

Ureter. Duct conveying urine from kidney to urinary bladder.

Urethra. Duct leading from urinary bladder to exterior.

Urinary Bladder. Sac storing urine.

Uriniferous Tubule. Narrow coiled tube of vertebrate kidney leading from Bowman's capsule to the collecting ducts which convey the urine to the ureter.

Uterine Tube. See *Fallopian Tube*.

Uterus. Womb. Muscular expansion of oviduct of female in which the embryo develops.

Utricle (Utriculus). See *Ear, Inner*.

Vagina. Channel of female connecting uterus with exterior via a short vestibule.

Vagus Nerve. Tenth cranial nerve. Mainly parasympathetic supplying esophagus, stomach, respiratory tree, and heart; and sensory, from, e.g., lungs and heart.

Vascular. Containing, or concerning, vessels which conduct fluid.

Vas Deferens. Tube in male conducting sperm from epididymis to urethra.

Vas Efferens. Tube (of which there are many on each side) conveying sperm from testis to epididymis.

Vasoconstriction. A reduction in the caliber of a blood vessel, particularly of the arterioles.

Vasodilatation. An increase in the caliber of a blood vessel.

Vasomotor. Influencing the movements of the walls of the blood vessels, particularly of the arterioles.

Vasopressin. See *Pitressin*.

Vein. Blood vessel carrying blood from the capillaries to the heart.

Vena Cava Inferior (Posterior Vena Cava, Postcaval Vein). Main vein of tetrapod vertebrates passing blood into the heart (right auricle) from veins of almost all body behind the forelimbs. A single median vein, largest in the body.

Vena Cava Superior (Anterior Vena Cava, Precaval Vein). Main vein of tetrapod vertebrates returning blood to the heart (right auricle) from the forelimbs and head. Usually a pair, but in many mammals, including man, only the right one persists in adult.

Venomotor. Influencing the movements of the walls of the veins.

Ventral. Situated at, or relatively nearer to, that side of the animal which, in those which walk on four feet, is normally directed downwards with reference to gravity. In human beings, ventral side is directed forwards. Opposite of dorsal.

Ventral Root (Anterior Root, Motor Root). Nerve root which is connected with spinal cord anteriorly or ventrally. Contains the motor fibers. Cf. *Dorsal Roots*.

Ventricle. (1) Chamber of the heart. Receives blood from an auricle and pumps it into arteries. Birds and mammals have two, right ventricle supplying blood to lung, left supplying rest of body. (2) Cavity within vertebrate brain filled with cerebrospinal fluid; lateral ventricles in cerebral hemispheres; third in rest of forebrain; fourth in medulla oblongata.

Venule. Small vein of vertebrates, differing from capillary by being of somewhat larger size and having more connective tissue in its wall. Collects blood from capillaries.

Vertebra. See *Vertebral Column*.

Vertebral Column. Backbone. Longitudinally arranged chain of bones (vertebrae) near dorsal side, surrounding spinal cord.

Vertebrata (Craniata). Most important subphylum of the Phylum Chordata. Contains the fish, amphibians, reptiles, birds, and mammals.

Villus. Finger-like projection. (1) *Intestinal villi* (about 1 mm. long in man), present in enormous numbers, give lining of small intestine velvet-like appearance. Each villus is covered by epithelium, contains blood vessels and a lacteal. Absorptive surface of intestine is thus immensely increased. (2) *Chorionic villi*. Projections of chorion (q.v.) in mammalian placenta which increase area of contact between embryonic and maternal tissues.

Virus. A member of a group of disease-producing agents which are parasitic in plants and animals. They are unable to multiply outside the host tissues, and some are so small as to pass through filters which retain bacteria.

Visceral. Pertaining to a viscus.

Viscus. Any organ in the interior of the body, especially in the body cavities.

Visual Purple. Compound of a protein with a prosthetic group of which

- Vitamin A is an essential precursor. Occurs in rods of vertebrate retina. Chemically changed (and bleached) by light, the change being basis of function of rods as light-sensitive receptors. Increases in amount in dark, raising sensitivity of rods to faint light (dark adaptation).
- Vitamin.** Dietary principle essential for the normal functioning of the body.
- Vitamin A.** A substance required by man. Fat soluble. Stored in liver. Deficiency in man causes night blindness (the vitamin being a constituent of visual purple) and keratinization of cornea, and other effects involving epidermis and nervous tissue.
- Vitamin B Complex.** Several water-soluble vitamins, formerly thought to be a single vitamin. See *Thiamin* (B_1), *Riboflavin* (B_2), *Pyridoxine* (B_6), *Pantothenic Acid*, *Nicotinic Acid*, *Cobalamine* (B_{12}).
- Vitamin C.** See *Ascorbic Acid*.
- Vitamin D.** A substance required by man, though some is synthesized. Fat soluble. Stored in liver. Deficiency in childhood causes rickets; in adults, sometimes osteomalacia. Effect of the vitamin is on absorption and deposition of calcium and phosphate. Synthesis in man is by action of ultraviolet (in sunlight) on a precursor in skin.
- Vitamin E (Tocopherol).** A substance required by vertebrates. Fat soluble. Deficiency may cause abortion in female and sterility in male.
- Vitamin F.** See *Linoleic Acid*.
- Vitamin K.** A substance required by man and other mammals. Fat soluble. Deficiency causes tendency to hemorrhage, since the vitamin takes part in synthesis of prothrombin in liver. Various slightly different compounds have Vitamin K activity. Part of human requirements probably comes from bacteria living in gut.
- Vitreous Humor.** Jelly-like material which fills cavity of vertebrate eye behind the lens.
- Viviparous.** Having embryos which develop within the maternal organism and obtain nutrients by close contact with maternal tissues, frequently by a placenta, without interposition of any egg membranes. Viviparity occurs in all placental mammals, and sporadically in other groups of animals.
- Vocal Cord.** See *Larynx*.
- Volt.** The unit of electromotive force, being the force required to cause a current of one ampere to flow through a resistance of one ohm.
- Voluntary Muscle.** See *Striated Muscle*.
- Wandering Cells.** Cells of blood and connective tissue which actively migrate *in vivo*, e.g., macrophages.
- White Blood Cell.** Blood cell containing no hemoglobin. Nucleated. Includes polymorphs, lymphocytes, and monocytes.
- White Matter.** Tissue of central nervous system, mainly formed of nerve fibers whose myelin gives it glistening white appearance. Glia and blood vessels also present. Lies as a layer outside gray matter and forms most of the tracts connecting different parts of the central nervous system.

X-Chromosome. A sex-chromosome. Unlike Y-chromosome, contains numerous genes which show sex linkage.

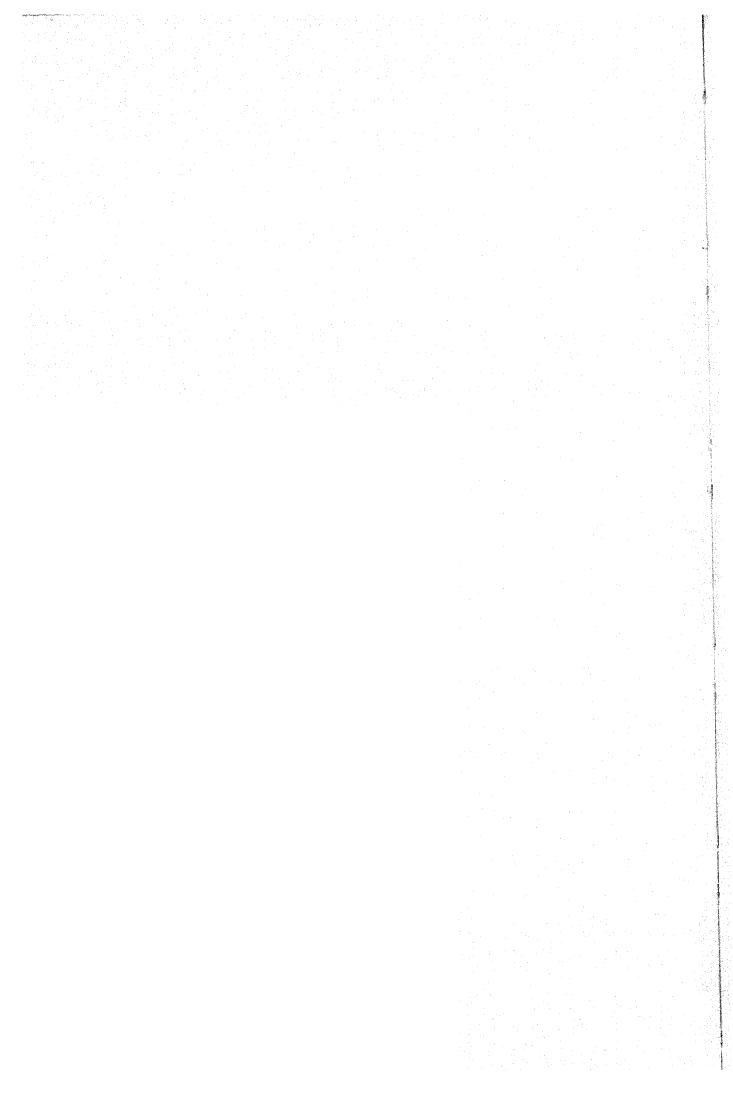
Y-Chromosome. A sex chromosome. Usually differs from the X-chromosome (q.v.) in size. Often, only a short part of it pairs with the X-chromosome at meiosis.

Yolk Sac. Sac containing yolk which hangs from ventral surface of very yolky vertebrate embryos (elasmobranchs, teleosts, reptiles, birds); or the homologous organ of mammals which is empty of yolk.

Zoology. Study of animals.

Zygote. The fertilized ovum, before it undergoes division.

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